Clinical Study Protocol

Drug Substance	Umbrella study
Study Code	D6185C00001 (HUDSON)
Version	14.0
Date	09 October 2024

An Open-Label, Multi-Drug, Biomarker-Directed, Multi-Centre Phase II Umbrella Study in Patients with Non-Small Cell Lung Cancer, who Progressed on an anti-PD-1/PD-L1 Containing Therapy (HUDSON)

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

Regulatory Agency Identification Numbers:

EudraCT number: 2017-002208-28

EU CT number: 2023-509004-15-00

IND number: 138050

VERSION HISTORY

Version 14.0, 09 October 2024

Key amendments and rationale for changes:

Section 4.4, end of study definition:

- "data cut-off" was updated to "database lock" throughout this section.
- Updated to state non-serious AEs would also be collected in patients who continue to receive treatment after database lock.

Section 7.2, lost to follow-up: Updated to state 2 attempts should be made when attempting to contact a patient who has missed a scheduled site visit.

Section 8.3.2, time period and frequency for collecting AE and SAE information: Updated to describe the collection of non-serious adverse events (AEs) and serious AEs (SAEs) in patients who continue to receive study treatment after final database lock and who are later discontinued from study treatment.

Section 8.3.13, safety data to be collected following the final database lock

- Title of the section was updated from "Safety data to be collected following the final data cut-off of each module" along with corresponding updates to the text.

Section 8.3.14, continued access to study intervention after the end of the study: This section was added to describe the continued supply of study treatment by the Sponsor to patients after data cut-off.

Section 8.4.1, reporting of serious adverse events:

- Addition of text clarifying that following the reporting of a SAE to the Sponsor by telephone, a paper SAE form should also be completed.
- Addition of text describing EU CTR SUSAR reporting process.
- Addition of text describing reporting of non-serious AEs and SAEs until the end of the post-trial access period.

Section 9.4.2, general considerations: Text describing the reporting of safety data in ongoing patients following the data cut-off in a modular CSR addendum or final CSR was deleted.

List of abbreviations was updated.

Minor text clarifications and corrections of typographical errors were also made.

Version 13.0, 14 December 2023

Key amendments and rationale for changes:

Front page: EU CT number added.

Section 1.2, synopsis:

- To update the estimated date of last patient completed.
- To align with the current version of the SAP, text has been updated to state that the efficacy endpoints for each non-matched cohort will be summarised by response assigned by the investigator.

Section 1.2, synopsis; Section 4.1.2, cohort naming conventions; Section 4.1.3, treatment groups: Updated to state that all modules that have been closed to recruitment.

Section 1.2, synopsis; Section 9.5, interim analysis: CCI [redacted]

Section 5.1, inclusion criteria; Section 8.8, biomarkers: Inclusion criterion #6 has been updated to clarify that a tumour sample taken within the previous 24 months is acceptable if taken after progression on prior anti-PD-(L)1 therapy; Section 8.8 has been updated accordingly.

Section 8.1.3.1, dosed patients; Section 9.4.2, general considerations: Updated to clarify the language on survival status and follow-up data collection.

Section 8.3.12, adverse events of special interest: Updated to reflect the new known adverse drug reactions as per the durvalumab IB Edition 19.

Section 8.4.4.1, timelines; Appendix A1, regulatory and ethical considerations; Appendix A6, dissemination of clinical data: Updated to align with the updated version of the CSP template.

Section 9.4.2, general considerations: Updated the language on the data analysis sets to align with the SAP.

Section 9.5.1, independent data monitoring committee (IDMC): Updated to clarify the frequency of the IDMC safety data reviews.

Minor text clarifications and corrections of typographical errors were also made.

Updates made to the CSP Modules where clarification of text is required per updates to the Core protocol, and clarification of existing text where needed (refer to respective modules for details).

Version 12.0, 01 March 2023

Key amendments and rationale for changes:

Section 1.2, synopsis; Section 4.1.2, cohort naming conventions; Section 4.1.3, treatment groups; Section 9.2, sample size determination: Updated to state the modules that have been closed to recruitment.

Section 1.2, synopsis; Section 9.5, interim analysis:

- Triggering points for Module 10 interim analysis were clarified. CCI [redacted]
- Text regarding Module 11 updated to clarify the number of confirmed responses needed to potentially expand the cohort.

Section 4.4, end of study definition; Section 7.3, withdrawal from the study; Section 8.4.4, medication error, drug abuse, and drug misuse; Appendix A1, regulatory and ethical considerations; Appendix A4, data protection; Appendix A7, data quality assurance; Appendix B8, medication error, drug abuse, and drug misuse: Updated to align with the updated version of the CSP template.

Section 4.4, end of study definition:

- End of study definition wording was updated to align with the updated version of the CSP template and clarify the LSLV definition.
- Text updated to clarify the reasons for entire study or individual cohorts' premature termination by AstraZeneca.
- Text updated to clarify that SAEs, pregnancy, and overdose occurring beyond the data cut-off will be reported in paper forms.

Section 5.2, exclusion criteria: Criterion 6 text updated to align with the updated version of the Durvalumab CSP template.

Section 5.2.1.3, consent based on biomarker status: Text updated to allow potential exemption from re-testing at the central laboratory for tissue samples from patients with local results generated in accordance with the protocols of CCI [redacted]

Section 5.4, screen failures: Text was updated to clarify the information that will be collected for screen failures.

Section 6, study treatments: Updated to clarify the location of the Toxicity Management Guidelines for trastuzumab deruxtecan and for durvalumab.

Section 8.1.3.1, dosed patients; Section 9.4.2, general considerations: The period for collection of survival data was clarified.

Table 5, laboratory safety variables:

- Inclusion of the coagulation parameters.
- Footnote d was updated to clarify that the evaluation of free T3, T4 and TSH is not required in Module 11.

Section 9.4.2, general considerations: Updated to align with Section 4.4.

Table 10, AZD6738 PK plasma sample schedule for patients receiving durvalumab plus AZD6738:

- Title was updated to correct the matrix of the PK samples.
- The window allowed to collect AZD6738 PK samples at Cycle 0 Day 7 and Day 28 was added to the footnote.

Table 11, durvalumab PK sample schedule for patients receiving durvalumab plus AZD6738: The footnote text was updated to clarify the timing of durvalumab PK sample collection and to clarify that samples should be collected from the opposite arm to that where the infusion was administered.

Minor text clarifications and corrections of typographical errors were also made.

Updates made to Modules 3, 5, 6, 7, 8, 9, 10 and 11 to align with current IB editions, where clarification of text was required per updates to the Core protocol, and clarification to existing text where needed (refer to respective modules for details).

Version 11.0. 16 August 2022

Key amendments and rationale for changes:

Addition of Module 11 (Group C; molecular aberration independent) to assess AZD6738 at a dose of 240 mg BD given orally (dosed for 7 days in each 4-week cycle) in monotherapy. CCI [redacted] List of appendices; Section 1.2, synopsis; Figure 1, study design; Section 4.1.1, modular protocol structure; Section 4.1.2, cohort naming conventions; Figure 3, schematic of the treatment naming conventions;; Figure 4, study flow diagram; Section 4.1.3, treatment groups; Section 4.1.4, Clinical screening procedures; Section 5.1, inclusion criteria; Section 5.2, exclusion criteria; Figure 5 footnote; Section 5.2.1.3, consent based on biomarker status; Table 5, laboratory safety variables, footnote h; Section 8.8, biomarkers; Section 9.2, sample size determination; Section 9.4.2, general considerations; Section 9.5, interim analyses.

The following sections are updated to describe the potential exemption for Modules 10 and 11 patients from requiring a new tumour biopsy sample during pre-screening if a tumour tissue sample is obtained after progression on prior anti-PD-(L)1 therapy and ≤ 3 months prior to pre-screening; a tumour sample taken within the previous 24 months is acceptable if no such sample is available. As the intent remains to collect biopsies for all patients to support the HUDSON study objectives, this option provides some flexibility, if needed, to assess these module objectives: Table 1, schedule of activities footnote g; Section 4.1.1, modular protocol structure; Section 4.1.4, clinical screening procedures; Section 5.1, inclusion criterion 6; Section 5.2.1.1; Section 8.8, biomarkers.

Section 1.2, synopsis; Section 2.1, study rationale; Section 2.2, background; Section 5.2.1.3, consent based on biomarker status: Text describing the patient populations to be assessed in the study is updated to include molecular aberration independent patients (Group C cohorts).

Figure 1, study design: Updated to remove details for survival follow-up of screen failures and treatment reallocation of patients in Modules 1 to 5, and associated footnotes (no longer applicable as of protocol v10.0).

Section 2.2, background: Text (… *especially in the relapsed setting*) is added to differentiate between the patient profile for whom currently targeted therapy has been approved and patients who have a similar profile but for whom no standard of care exists. Text (…*in the previous untreated setting*) is added to clarify the regulatory authority approved indications for tyrosine kinase inhibitors.

Section 4.1.3, treatment groups: CCI [redacted] text is clarified to state that enrolment to molecular aberration independent cohorts will be prioritised over other modules and will be sequential.

Section 4.2.3, rationale for study design: Specific rationale for addition of Modules 10 and 11 is added.

Section 5.2, exclusion criterion 1; Section 5.2.1.3, consent based on biomarker status: Updated to add reference to Modules 10 and 11 that enrolled patients can proceed to main screening without waiting on central test results for pre-defined molecular aberrations. **This decision has been made by the sponsor to allow patients in these modules to start study treatment without waiting for the prospective central testing results when recruitment is only open to Group C modules.**

Section 5.2.1, two-step consent process: text is updated to clarify patient stratification based on confirmation of biomarkers does not include Group C cohorts. **Table 5, laboratory safety variables:** Addition of lymphocyte and neutrophil counts to the haematology footnote to clarify these will be recorded for Modules 3, 10 and 11 as part of the routine white cell count for safety assessment. The footnote text related to retrospective recording of counts for Module 3 patients is also updated to align with the current SAP.

Section 8.4.3, overdose: text is clarified to state possible symptoms of overdose are not established **for any other agent studied** (in addition to durvalumab).

Section 8.8.1.2, Collection of new tumour samples: Additional information is included for the collection of optional biopsies at disease progression, to emphasise the importance of sample collection for this exploratory research.

Section 8.8.2, collection of plasma samples of CCI [redacted] **Section 8.8.3, collection of blood samples to assess immune status**: Sections are updated to provide further details and clarification of exploratory analyses to be performed.

Table 15, study analysis population: Footnote is added to clarify how analysis sets are to be defined. This is to align with the current statistical analysis plan.

Section 9.4.1, definition of endpoints (progression free survival): Text related to the timing of patient censoring is updated to align with the current statistical analysis plan.

Section 9.4.2, general considerations:

- Text is updated to clarify Group C Module 10 data will be summarised by dose group and resistance status while Module 11 data will be summarised together.
- Text describing the use of a modified RECIST 1.1 approach complementary to standard RECIST 1.1 for summarising efficacy variables is deleted as this is not efficient for capturing tumour inflammatory reaction and is no longer used.
- Subheadings (for Groups A/B and Group C) are added for readability.

Section 9.4.6, safety analyses: Text describing analysis of AE data for re-allocated patients is updated to align with the current statistical analysis plan.

Restructure of section content, deletion of duplicate text and addition of subheadings to improve readability: Section 1.2, synopsis (sections on number of patients and sample size); Section 4.1.1, modular protocol structure; Section 4.1.3, treatment groups; Section 9.2, sample size determination; Section 9.4.2, general considerations; Section 9.5, interim analyses.

In addition, minor typographical errors have been corrected throughout the core protocol where applicable.

Updates made to Modules 3, 8, 9 and 10 where clarification of text is required per updates to the Core protocol, and clarification to existing text, where needed (refer to respective modules for details).

Version 10.0, 12 April 2022

Key amendments and rationale for changes:

Addition of Module 10 (Group C; molecular aberration independent) to further assess the efficacy, safety, and tolerability of durvalumab + AZD6738 in 2 cohorts at 160 mg and 240 mg BD (dosed for 7 days in each 4-week combination cycle). Exploratory PK

analyses will also be conducted. CCI [redacted] List of appendices; Section 1.2, synopsis; Figure 1 footnote, study design; Section 3, study objectives; Section 4.1.1, modular protocol structure; Section 4.1.2, cohort naming conventions; Figure 4, study flow diagram; Section 4.1.3, treatment groups; Section 5.2.1, two-step consent process and Figure 5 footnote; Table 5, laboratory safety variables; Section 8.5, pharmacokinetics (including new Tables 10 and 11); new Table 13, ADA blood sample schedule for durvalumab (Module 10 only); Section 8.6, pharmacodynamics; Section 9.4.7.2, pharmacokinetic analyses; Section 9.2, sample size determination; Section 9.4.7.2, pharmacokinetic analyses; and Section 9.5, interim analyses.

Two exploratory objectives added to investigate CCI [redacted] **This change is to align with CSR Module 2 and SAP v5.0:** Section 1.2, synopsis; Section 3, objectives and endpoints; Section 9.4.1, definition of endpoints. **Exploratory objective added to quantify** CCI [redacted] **This change is to further explore the tumour response by characterising** CCI [redacted] Section 1.2 synopsis and Section 3 objectives and endpoints.

Text updated to clarify survival follow-up of pre/main screen failures is no longer required from implementation of protocol v10.0 as sufficient data have now been collected to investigate the outcome in these patients: Table 1, schedule of activities; Section 1.2, synopsis; Figure 1, study design; Section 3, objectives and endpoints; Section 4.1.4, clinical screening procedures; Section 5.4, screen failures; Section 8.1.3.2, screen fail patients; Section 9.4.2, general considerations.

Increase in size of each expanded biomarker non-matched cohort (B.3.ACQ and B.3.PRI) in Module 3 to include up to approximately C [redacted] **more patients (to a total of approximately** C [redacted] **patients per cohort). This change is to support recruitment to the ATM biomarker matched cohort (A.3.ATM), which is also re-opened and expanded to an approximate total of** C [redacted] **patients**: Section 1.2, synopsis; Section 4.1.1 modular protocol structure; Section 4.1.3 treatment groups; Section 9.2, sample size calculation.

Optional re-allocation to different treatment cohort (Modules 1 to 5 only). Text added to state from implementation of protocol v10.0, re-allocation of patients is no longer applicable. CCI [redacted] Table 1, schedule of activities; Figure 1, study design, footnote; Section 5.2.1.2, main screen consent; Section 7.4, optional re-allocation to different treatment cohort (Modules 1 to 5 only).

Text updated to state recruitment to Modules 2, 5, 8 and 9 is closed, and recruitment to Module 3 has been re-opened and expanded. CCI [redacted] Section 1.2 Synopsis; Section 4.1.1, modular protocol structure; Section 4.1.2, cohort naming conventions; Figure 4, study flow diagram footnotes; Section 4.1.3, treatment groups; Section 9.2, sample size determination.

Table 1, schedule of activities:

- Time window widened by +2 weeks for screening hepatitis B and C, and HIV tests, if agreed with the study physician, to avoid unnecessary repeat testing if these are performed outside the window.
- New footnote g added for Module 10 patients: If in agreement with the sponsor, patients may be exempt from providing a new tumour biopsy during pre-screening if a tumour sample obtained ≤1 year is available to confirm eligibility for the study.

Table 3, study objectives and endpoints/variables: Endpoint/variable text expanded for the exploratory objectives 'To investigate cancer-relevant immune status' and 'To investigate changes in cancer-related gene mutation and aberrations', to provide further specifics for the biomarker analyses and clarity.

Section 1.2, synopsis: Estimated date of last patient completed has been updated and text related to the closed Module 9 (treatments and duration) deleted to remove duplication or where it is no longer required.

New Section 4.1.6, study conduct mitigation during study disruptions due to cases of civil crisis, natural disaster, or public health crisis: Added to clarify potential mitigation procedural changes related to the COVID-19 pandemic.

Section 4.2.3, rationale for study design: Exploratory biomarker text updated to clarify that investigations may also include pharmacodynamic profiles.

Section 4.1.4, clinical screening procedures; Section 5.1, inclusion criteria (IC 6) and Section 8.8, biomarkers: Text added to clarify that for Module 10 only, and in agreement with the sponsor, patients may be exempt from a tumour biopsy during pre-screening if a tumour sample obtained ≤1 year is available to confirm eligibility for the study.

Section 5.2, exclusion criteria: criterion 15 updated to add guidance for use of authorised/approved COVID-19 vaccines, to align with the COVID-19 vaccination guidance letter (dated 24 Feb 2021) provided to sites.

Section 7.1, discontinuation of study treatment, Section 8.1.1, tumour assessments by CT or MRI scans, Appendix G 4.1, schedule of evaluation: Text added to clarify patients

with radiological disease progression who have clinical benefit and remain on study treatment will continue to receive radiological scans per protocol.

Section 7.1.2, procedures for discontinuation of study treatment: Text clarified for when study treatment is to be returned at the study drug discontinuation visit.

New Section 8.1.2.1 added for CCI [redacted] **for exploratory analysis:** To align with addition of the exploratory objective for quantifying CCI [redacted]

Section 8.1.3.1, dosed patients: Timing of safety follow-up clarified.

Table 5, laboratory safety variables: Eosinophils and monocytes with associated footnote added for collection in the Module 3 expanded cohorts, as monocytes and potentially eosinophils appear to have a role in the mode of action of AZD6738. Text also clarified in Section 8.2.1 to replace 'infusion' with 'dosing' as not all modules use infusions.

Section 8.3.11, deaths: Text for reporting death resulting from disease progression to the study physician at the next monitoring visit removed as this is not required.

Section 8.6 pharmacodynamics: Details included of exploratory pharmacodynamic parameters to be analysed in Modules 3, 8, 9 and 10 (and other modules where feasible).

Section 9.2, sample size determination; Section 9.4.2, general considerations; Section 1.2, synopsis: Text added to include analysis can be carried out once the final patient is dosed in a cohort if enrolment ends early.

Table 15, study analysis populations: Table updated to align with definitions in SAP v5.0.

Section 9.4.2, general considerations: Text added to clarify handling of safety data for re-allocated patients and to clarify the planned analysis if cohorts have patients ongoing on treatment after the data cut-off for the module CSR.

Section 9.4.5.2, analysis of the secondary variables: To align with the SAP v5.0, text for progression free-survival and overall survival analyses has been updated to state corresponding CCI confidence intervals will be provided for the interim analysis CCI [redacted]

Section 9.4.6, safety analyses: To align with the SAP v5.0, the definition of TEAEs and AEs occurring within the 90-day follow-up period has been updated.

In addition, minor typographical errors have been corrected throughout the core protocol where applicable.

Updates made to Modules 1, 3, 5, 7, 8 and 9 to align with current IB editions and Project Specific Safety Requirements, where clarification of text was required per updates to the Core protocol, and clarification to existing text where needed (refer to respective modules for details).

Version 9.0, 14 May 2021

Key amendments and rationale for changes:
The version number of this core CSP has been revised in line with Modules 8 and 9 in the HUDSON study; however, no changes have been made to the Core CSP, nor to Modules 1 to 7. Changes made to Version 8.1 and 9.0 of Modules 8 and 9 are detailed in the version history section of the respective modules, and summarised below:

Modules 8 and 9 were amended to add additional safety assessments based on reported adverse events of Grade ≥ 3 haematological toxicity including: anaemia, thrombocytopenia, neutropenia across studies in the AZD6738 programme, as summarised in the Urgent Safety Measures notification (date 22APR2021) and Investigator letters (15APR21, 16APR21, and 14MAY21).

These safety assessments are based on reported adverse events of Grade ≥ 3 haematological toxicity including: anaemia, thrombocytopenia, neutropenia (including a Grade 3 febrile neutropenia in one patient) in C patients, out of a total of C patients, who received AZD6738 using the 240 mg BD dose (2 weeks on and 2 weeks off in a 4-week cycle) across two ongoing AZ sponsored studies, as of 15APR21 (PLANETTE [D5339C00001; CCI patients]) and HUDSON [Module 8 and Module 9; CCI patients]).

Update to Module 8 to add additional haematological, clinical chemistry and vital signs monitoring visits on Day 8 (± 1 day window) of Cycles 1 and 2 to monitor toxicity, with the possibility of including the additional haematology and clinical chemistry monitoring visits in subsequent cycles later in treatment, as clinically indicated: See Table 1 and Section 6.6 of Module 8 for details.

Update to Module 8 to add emerging data from Module 3 of HUDSON and rationale for assessing AZD6738 monotherapy in Module 8): See Section 2.2.1.4 of Module 8 for details.

Update to Module 9 to add additional haematological, clinical chemistry and vital signs monitoring visits on Day 22 (± 1 day window) of Cycles 1 and 2 to monitor toxicity, with the possibility of including the additional haematology and clinical

chemistry monitoring visits in subsequent cycles later in treatment, as clinically indicated: See Table 1 and Section 6.6 of Module 9 for details.

Update to Module 9 to add emerging data from Module 3 of HUDSON and rationale for assessing AZD6738 monotherapy in Module 8): See Section 2.2.1.4 of Module 8 for details.

Update to Module 9 to add that the maximum interruption or cycle delay has been extended from 28 days to 42 days to permit a delay in the onset of the AZD6738 dosing. The change is to ensure that there are correct re-treatment conditions for AZD6738: See Section 6.6 of Module 9 for details.

Version 8.0, 11 September 2020

Key amendments and rationale for changes:

Addition of Module 9 to assess Durvalumab + AZD6738 (AZD6738 dosed for 14 days [from Days 15 to 28] in each 4-week cycle): Synopsis, Section 4.1.1, Section 4.1.2, Figure 4, Section 4.1.3, Table 10, and Section 9.2. Changes also made to these sections to clearly distinguish the other modules that include AZD6738.

Removal of web link to the durvalumab toxicity management guidelines as this website has been decommissioned. The toxicity management guidelines will instead be provided to sites: List of appendices, Section 4.1.1, Section 6, Section 7.1.1, and Section 8.4.5.

Figure 1: Footnote added to clarify that additional screening assessments for Module 6 can be found in the module, for consistency.

Table 2: Updated to reflect emerging observations on the frequency of molecular aberrations.

Section 3 Objectives and endpoints (and synopsis): Safety objective updated to cover all safety assessments being conducted in all modules. Last exploratory endpoint updated to allow exploratory work to be conducted to understand, among others, CCI

Section 5.1 Inclusion criteria: Inclusion criterion 9 – minor update to change > 3 weeks to ≥ 3 weeks to clarify that the treatment-free interval is a minimum of 3 weeks.

Section 5.2 Exclusion criteria: Exclusion criterion 7 – update to align with changes made elsewhere during CSP version 7.0 (use of highly effective birth control for 7 months after the last dose for females). Also updated in Section 5.3.

Section 8.1.1 Tumour assessments by CT or MRI scan: Update to clarify that the timing of tumour assessments applies unless otherwise specified in the SoA of the modules.

Section 8.1.3 Survival assessment: Consistency updates to align with Section 9.4.2.

Section 8.2.3 Vital signs: Updated to remove an inconsistency.

Section 8.2.5 Performance status: Updated to remove a redundant sentence.

Section 8.5.3 Other assessments – anti-drug antibody samples: Neutralising antibodies removed as they are not being assessed. ADAs continue to be assessed.

Section 9.4 Statistical analyses (9.4.1 Definition of endpoints, 9.4.2 General considerations 9.4.4 Exposure, 9.4.5.2 Analysis of secondary variables, and 9.4.6 Safety analyses) (and synopsis): Updates to align with the SAP.

Section 9.4.7.3 Anti-drug antibodies against durvalumab, AZD9150 or trastuzumab deruxtecan: Neutralising antibodies removed as they are not being assessed. ADAs continue to be assessed.

Version 7.0, 21 May 2020

Key amendments and rationale for changes:

Updates to Module 6 to address COVID-19-specific safety concerns: See Module 6 for details.

Addition of Module 8 to assess AZD6738 monotherapy: Synopsis, Section 4.1.2, Figure 4, Section 4.1.3.

Recruitment to Cohort B.5.PRI stopped: Synopsis, Section 4.1.1, Section 4.1.2, Figure 4, Section 4.1.3.

Section 3 Objectives and endpoints: New exploratory objective added to allow collection of samples that may be analysed for markers that correlate with clinical benefit and tolerability. (Also applies to the synopsis)

Section 5.2 Exclusion criteria:

- Exclusion criterion 8: Addition of the text in bold CCI [redacted] Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients, **or history of severe hypersensitivity reactions to other monoclonal antibodies**.
- Exclusion criterion 10 amended to allow more flexibility in recruitment in patients with brain metastases.

Section 5.3 Lifestyle restrictions: Revised the timeline for egg donation from 90 days to 7 months after the final dose of study drug per request from regulatory agencies. Consequently, alignment of timeline for female contraception from 6 months to 7 months after the final dose of study drug.

Section 8.2.1.2 Other safety assessments: Updated to clarify that tests will be performed by the local laboratory (removal of text suggesting this had to be a hospital laboratory).

Section 8.3 Collection of adverse events: Statement that confirmed or suspected COVID-19 events must be recorded on the eCRF.

Section 8.5 Pharmacokinetics: Addition of text providing instructions of additional PK samples to be taken for patients in Module 6 who receive chloroquine or hydroxychloroquine.

Section 8.5.3 Other assessments – anti-drug antibody samples: Addition of Module 5 to Table 10 to correct an error.

Section 9.4.2 General considerations: Changes made to clarify the timing of the analysis.

Section 9.4.4 Exposure: Removal of the equation to be used to calculate total exposure, as this will be provided in more detail in the SAP.

Section 9.4.6 Safety analyses: Update to the definition of a TEAE.

Section 9.4.7.2 Pharmacokinetic analyses: Addition of statement that plasma or serum concentrations of trastuzumab deruxtecan, durvalumab (for Module 6), and cediranib (for Module 7) will be measured. To correct an omission during the initial drafting of these modules during CSP version 6.

Version 6.0, 05 November 2019

Key amendments and rationale for changes:

Addition of Module 6 to assess durvalumab in combination with trastuzumab deruxtecan (DS-8201a) and Module 7 to assess durvalumab in combination with cediranib (AZD2171): Section 1.1, Table 1, Synopsis, Table 2, Section 4.1, Table 3, Section 5.2.1, Figure 4, Section 8.5, Section 8.5.3, Section 9.5.1.

Table 1 Schedule of Activities: Footnote added that screening results obtained >28 days before the first dose of re-allocated therapy should be discussed with the study physician. Footnote added that ad-hoc collection of survival status may be requested for OS analyses. Clarification that for Module 6, additional main screening assessments are detailed in Module 6 Table 1.

Table 1 and throughout: Re-allocation will be restricted to patients in Modules 1 to 5. Re-allocation will not be offered from Module 6 onwards, to minimise the complexity of the study and reflects that few patients to date have taken the opportunity for re-allocation to a second treatment combination.

Table 3 Study objectives and endpoints, Section 8.5.3, and Section 9.4.7.3: Removal of ADA testing for oleclumab, due to the data providing limited information to the oleclumab programme and to reduce the blood sampling burden for patients. Addition of ADA sampling for trastuzumab deruxtecan due to the addition of Module 6. Addition of PK sampling for trastuzumab deruxtecan and durvalumab (Module 6) and cediranib (Module 7).

Section 4.1.4 Clinical screening procedures: An interactive response technology (IRT) system is added in this protocol amendment for assignment of the unique E code and patient number, and cohort allocation based on the tumour biomarker results. Confirmation that if there is not an open cohort for which patient is eligible, the patient will be a pre-screen failure. Added a sentence that pre-screening is restricted to 6 months.

Section 5.2 Exclusion criterion 6: Active tuberculosis added to the exclusion, aligning with the latest safety information for durvalumab.

Section 5.2 Exclusion criterion 23: History of active primary immunodeficiency added to align with the latest safety information for durvalumab.

Section 5.3 Lifestyle restrictions: Addition of a restriction on females donating eggs while on study and for 90 days after the final dose of any study drug.

Section 8.1.1 Tumour assessments by CT or MRI scans: Added clarification that duplicates of radiological examinations must be available at site as the HUDSON Steering

Committee requested that scans are available for examination on request. This change will apply only to newly consented or re-consented patients (ie, not retrospectively).

Section 8.1.3.1 Dosed patients, Section 8.1.3.2 Screen fail patients, and Table 1: Statement added that ad-hoc collection of survival status may be requested for overall survival analyses, to enable interim decision making on a cohort based on the OS endpoint.

Section 8.2.4: Electrocardiogram: Guidance on the procedures to be followed in case of clinically significant ECG abnormalities including an ECG that demonstrates a QTcF value > 500 msec added.

Section 8.3.4 Adverse event data collection: Administration of treatment for an adverse event has been added to the list of information to be collected.

Section 8.3.7 Adverse events based on examinations and tests: Added clarification round the circumstances in which laboratory values should be reported as adverse events.

Section 8.3.12 Adverse events of special interest: section added to reinstate the durvalumab AESI information that was removed from Appendix H in the last amendment.

Section 8.3.13 Safety data to be collected following data cut-off of each module: Section added to provide instruction as to the procedures to follow once data cut-off of a module is reached.

Section 8.4.2.2 Paternal exposure: Updated from 90 days to 6 months the timeframe males should refrain from fathering a child or donating sperm, to correct an error.

Section 9.2 Sample size determination: CCI [redacted] Added statement that other efficacy endpoints including OS at 6, 9 and 12 months may be used to inform expansion decisions, but this has not formed part of the sample size calculations.

Section 9.4.6 Safety analyses: Definitions of TEAEs clarified for re-allocated patients.

Appendix A.5 Committees structure: Addition of a Safety Review Committee for modules containing a safety run-in.

Appendix A.10 Site closure: Further information on procedures to be followed in the event of site closure added, for clarification.

Appendix C3 International Airline Transportation Association (IATA) 6.2 Guidance Document: Update of a web address.

Version 5.0, 19 March 2019

Key amendments and rationale for changes:

Updated primary statistical analysis from modified RECIST 1.1 to RECIST 1.1. To ensure comparability with other NSCLC study results, the analysis is reverting from modified RECIST 1.1 to RECIST 1.1. Amended in the following: **Table 1 Schedule of Activities – pre-screening and main screening visits**, **Synopsis**, **Table 3 Study objectives**, **Section 7.1 Discontinuation of study treatment**, **Section 7.4 Optional re-allocation to different treatment cohort**, **Section 8.1.1 Tumour assessments by CT or MRI scans**, **Section 8.1.2 Tumour evaluation**, **Section 9.4.1 Definition of endpoints**, **Section 9.4.2 General considerations**, and **Appendix G Guidelines for evaluation of objective tumour response using RECIST 1.1 criteria (Response Evaluation Criteria in Solid Tumours).**

Table 1 Schedule of Activities – pre-screening and main screening visits: Footnote 'e' added to describe which assessments are required for screening of patients re-allocated to a different treatment cohort.

Synopsis and **Table 3 Study objectives:** Noted that AZD9150 is also known as danvatirsen, in line with the Investigator's Brochure.

Figure 1 Study design: Updated to clarify that patients with locally advanced disease are included, CCI at pre-screening.

Section 4.1.4 Clinical screening procedures: Clarified that only patients who are strongly suspected to have disease progression (based on clinical and radiological features as determined by the investigator) or are experiencing disease progression should be enrolled. If the investigator is considering another treatment at this stage, the patient should not be enrolled in the HUDSON study.

Section 5.1 Inclusion criteria and **Section 5.2 Exclusion criteria:** Sentence added to note that specific module criteria should be followed if these are more stringent than the core criteria. Also clarified in **Section 8.2.1.1 Coagulation**.

Section 5.1 Inclusion criteria (Criterion 5): Clarification on the required prior treatment, in response to questions from investigators. According to the study's main objective, patients must have had disease progression on a prior anti-PD-1/PD-L1 therapy. The patient must have also received a prior platinum doublet though it is not required to have had disease progression whilst receiving treatment with the platinum doublet therapy.

- The following sections were amended in line with the updated inclusion criterion 5: Synopsis, Section 2.1 Study rationale, 2.3 Benefit/risk assessment, 4.1 Overall design, 4.1.2 Cohort naming conventions, and 4.2.2 Rationale for conducting this study.

Section 5.1 Inclusion criteria (Criterion 10): The protocol steering committee has advised that patients with significant weight loss should be excluded from protocol treatment due to an adverse risk-benefit.

Section 5.2 Exclusion criterion (Criterion 10): Updated in response to queries from investigators, to exclude patients with unstable brain metastases as these patients are best managed outside of the current study with standard-of-care (as clinical management is more complex). Disease stability is best demonstrated by imaging rather than symptoms.

Section 5.2 Exclusion criterion (Criterion 16): Clarification of the number of prior lines of anti-PD-1/PD-L1 therapy in response to questions from investigators.

Figure 5 Schematic of the two-step consent process: updated to clarify that consent is required for the collection of a plasma CCI sample to provide tumour samples for central molecular analysis.

Section 5.2.1.3 Consent based on biomarker status: Clarification that if a patient has more than one identified biomarker for a biomarker-matched cohort, he/she may be allocated to the next matched cohort based on the pre-defined algorithm.

Section 5.4 Screen failures: 'Number code' replaced by 'E-code' to avoid confusion with the Patient number provided prior to dosing.

Section 7.1 Discontinuation of study treatment: Clarification that patients with disease progression per RECIST 1.1 may continue treatment if none of the other discontinuation criteria are met. Patients with symptomatic deterioration described under a separate bullet.

Section 7.1.1 Treatment interruption: Section header and text changed from 'temporary discontinuation' to 'treatment interruption' for clarity.

Section 7.3 Withdrawal from the study, **Section 8.8.7 Withdrawal of informed consent for donated biological samples** and **Appendix C Handling of human biological samples:** Reference made to the withdrawal consent checklist.

Section 7.4 Optional re-allocation to different treatment cohort: Clarification of the patient re-allocation procedure.

Section 8.1.1 Tumour assessments by CT or MRI scans, **Section 8.1.2 Tumour evaluation** and **Appendix G Guidelines for evaluation of objective tumour response**

using RECIST 1.1 criteria (Response Evaluation Criteria in Solid Tumours): Clarification of confirmatory scan procedure.

Table 5 Laboratory safety variables: S/P-Calcium amended to S/P-Total Calcium.

Section 8.2.2 Physical examinations: Deletion of a duplicated word.

Section 8.2.3 Vital signs: Amended to allow additional pulse and blood pressure measurements, should they be required to confirm true readings in cases of patient anxiety.

Section 8.3.2 Time period and frequency for collecting AE and SAE information: Adverse events/serious adverse events will be collected for 90 days following discontinuation of study treatment as is customary for regimens containing treatment with immuno-oncology drugs. However, the adverse event profile will be confounded by any anticancer treatment initiated after HUDSON treatment is permanently discontinued. For this reason, only events causally related to HUDSON treatment need to be reported when another anticancer treatment is initiated. This is to avoid reporting adverse events that are related to the anticancer treatment following HUDSON treatment, as this is not the objective of the study. This does, however, allow for the reporting of delayed effects related to HUDSON treatment.

Section 8.4.5 Management of study drug-related toxicities: Additional guidance added for management of toxicities.

Section 8.4.5 Management of study drug-related toxicities and **Appendix H Toxicity management guidelines for durvalumab:** Clinical study associate amended to clinical research associate.

Section 8.8.3 Collection of blood samples to assess immune status: Section header corrected for clarity.

Section 8.8.7 Withdrawal of informed consent for donated biological samples: Process order amended for clarity.

Section 9.4.1 Disease control rate: the definition of DCR to be evaluated at both 12 and 24 weeks was updated in line with AstraZeneca Early Clinical Development guidance text.

Appendix E Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law: Appendix updated following an update to AstraZeneca internal procedures.

Appendix H Toxicity management guidelines for durvalumab: The Toxicity Management Guidelines (TMGs) for durvalumab have been removed from the main body of the durvalumab CSP template and moved to a standalone annex. TMG versioning will be

independent of the protocol allowing for consistency across the durvalumab clinical development program. Updated in: **List of Appendices**, **Section 4.1.1 Modular protocol structure**, **Section 6 Study treatments**, **Section 7.1.1 Temporary discontinuation**, **Section 8.4.5 Management of study drug-related toxicities**.
Version 4.0, 26th October 2018
Key amendments and rationale for changes: **Table 1 Schedule of Activities**: clarification of footnote stating that main screening assessments performed within 3 days prior to first study need not be repeated on C1D1 or C0D1 pre-dose unless the treating physician deems them clinically necessary. **5.1 Inclusion criteria:** 4. This criterion was clarified to confirm that patients need to have metastatic *and* recurrent NSCLC. In addition to metastatic disease, patients with locally advanced disease in the absence of distant metastases can be considered. 5. Clarification that patients may be considered if they have had an anti-PD-1/PD-L1 and a platinum doublet regimen for locally advanced NSCLC, in the absence of distant metastases. This change is in line with treatment practices where some patient with locally advanced disease not amenable to curative therapy is treated as patients with metastatic disease. **Section 7.4 Optional re-allocation to different treatment cohort:** clarified that allocation to an alternative treatment cohort will be informed by molecular testing of the tumour sample acquired prior to first HUDSON treatment and/or at disease progression so patient re-allocation is not delayed by waiting for the results from the biopsy taken at progression. **8.8.1.2 Collection of new tumour samples:** clarification of the requirement for fresh tumour biopsy, with fresh frozen sample to be frozen whenever feasible (1 sample) and ≥3 cores to be formalin-fixed paraffin-embedded (FFPE) in each block. **Section 9.5.1 Committees structure and Appendix A5:** Addition of an independent data monitoring committee (IDMC) to provide an assessment of safety for the HUDSON study.
Version 3.1, 31 July 2018
Key amendments and rationale for changes:

Addition of Module 5 to assess durvalumab in combination with oleclumab (MEDI9447): Synopsis, Section 4.1.2, Figure 4, and Section 4.1.3.

Update to reflect the decision to stop recruitment to Module 4 due to lack of efficacy in the vistusertib clinical programme: Sections 1.2, 4.1.1, 4.1.2, and 4.1.3

Table 1 Schedule of Activities:

- Removal of the requirement for allocation to treatment cohort and starting treatment to occur on the same day.
- CCI [redacted]
- Blood sample for CCI [redacted] molecular assessment moved from main screen to pre-screen to allow exploration of outcomes based on plasma ctDNA molecular profile for potential patient allocation (Section 8.8 also updated to clarify that this sample is mandatory).

Exploratory objectives (Synopsis and Table 3):

- Addition of CCI [redacted] limited to the analysis of CCI [redacted] to allow exploration of the CCI [redacted]
- Added explanation that outcomes in screen fail patients will be grouped by cancer-related molecular changes as determined by tissue or plasma CCI [redacted] results.

Estimated date of last patient completed: Extended to Q3 2021 due to the addition of Module 5.

Section 4.1.3 Treatment groups: An explanation of how the sequential order of the biomarker non-matched cohorts will be performed has been added.

Section 4.1.4 Clinical screening procedures: Text added to clarify screening procedures.

Section 4.1.5 Regulatory amendment for additional modules: Removal of Canada-specific text, as the process for Canada will now follow the process for Europe and the Rest of the World.

Inclusion criterion 6: Updated to permit provision of tumour biopsies obtained within approximately 3 months of main screen consent, to ensure patients are not excluded when just outside this window.

Inclusion criterion 8: Updated to allow previously irradiated lesions to be considered a target lesion if the lesion has progressed (Appendix G was also updated accordingly).

Exclusion criterion 11: Criterion deleted to allow patients with pre-existing renal disease to enter the study. Evolving safety information has established that provided the creatinine clearance is adequate as per exclusion criterion 18, the general exclusion of such patients is no longer required.

Exclusion criterion 13: Amended to allow patients to receive bisphosphonates or RANKL inhibitors for the treatment of bone metastases.

Exclusion criterion 15: Amended to extend the period patients should not receive live vaccines to 180 days after the last dose of study drug. Updated for consistency across all modules of the study.

Section 5.2.1.1: Patients to be given the choice of undergoing the main screening assessments before the biomarker results are known, in order to shorten the waiting time before treatment.

Section 5.2.1.3: The HUDSON clinical trial assay uses a subset of the FoundationOne CDx assay. Where a patient has a pre-existing FoundationOne CDx result, no additional tissue will be used for retrospective confirmation.

Section 7.1.1 Temporary discontinuation: Text moved from individual modules and amended to allow patients to continue receiving treatment with monotherapy if, in the opinion of the treating physician, they are deriving benefit.

Section 7.1.2 Procedures for discontinuation of study treatment: Details regarding the timing of the drug discontinuation visit added.

Section 7.4 Optional re-allocation to a different treatment cohort: Clarification of SoA activities when patients are re-allocated.

Table 8 ADA blood sampling schedule for durvalumab: Update to the durvalumab ADA sampling schedule CCI Sampling is still required pre-dose on Cycle 1 Day 1 and Cycle 2 Day 1, but is now also subsequently required Q12W within the first year and Q24W in the second year of treatment. Information on the timing of ADAs for oleclumab in Module 5 added.

Section 9.4.2 General considerations: Added that in addition to the summaries using modified RECIST v1.1, efficacy variables will also be summarised using a standard RECIST v1.1 approach. The additional analyses will provide a sensitivity analysis to summaries using modified RECIST v1.1.

Appendix A10: Addition of site closure conditions as per ICH GCP E6 section 6.9.4 Criteria for the termination of the trial.

Version 2.0, 26 February 2018

Key amendments and rationale for changes:

IND number updated following advice from the FDA to conduct HUDSON under its own IND, which cross references IND 119833.

Synopsis - Treatments and treatment duration: Updated following confirmation of the recommended phase II dose for vistusertib.

Table 1 Study of Activities – pre-screening and main screening visits:

- Clarified that the archival biopsy should be the most recent sample.
- Corrected the section to refer to for blood CCI as section 8.8.2 and for tumour evaluation as section 8.1.1.

Figure 1 Study design: For patients who are re-allocated to a second treatment within HUDSON, the "screening assessments as per schedule of assessments in the treatment specific module" was corrected to state "as per schedule of assessments **in the core protocol"**.

Removal of CCI throughout the protocol: Based on observations from other studies exploring the hypothesis CCI have been removed as biomarkers of interest in HUDSON. This change was made in the following places:

- **Table 2 Molecular aberrations:** the prevalence CCI alone was added.
- **Figure 4 Study flow diagram:** CCI
- **4.1.3 Treatment groups** - Group A: Biomarker matched

Clarified that the archival sample can be sent to the central lab for molecular profiling prior to radiological progression on prior therapy in sections **4.1.3 Treatment groups** - Group B: Biomarker non-matched, **4.1.4 Clinical screening procedures** and **5.2.1 Two-step consent process.**

4.1.5 Regulatory amendment for additional modules: Added the requirement in Canada to submit separate amendments for module 2, module 3, module 4, and any future modules.

4.4 End of study definition: Clarified that patients may continue to receive study treatment following discussion with, and approval from the sponsor.

5.1 Inclusion criteria: added a reference to section 8.8.1.2 to provide further information to criterion 8 on choice of lesion and whether is can be used for a biopsy.

5.2 Exclusion criteria:

- **Updated the list of genetic alterations** to include targetable alterations in *EGFR*, *ALK*, *ROS1, BRAF, MET* and *RET*, as per NCCN guidelines version 2.2018.

- **Prior/concomitant therapy:** Updated in line with the new durvalumab IB Edition 12 to state that local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable.
  - **Exclusion criterion 18f**, clarification that the Cockcroft-Gault equation will be utilised at screening to determine eligibility, considering the Cockcroft-Gault equation is a more reliable indicator of renal function than creatinine alone. Patients with a creatinine clearance ≤40 mL/min, calculated by the Cockcroft-Gault equation, are not eligible. Where creatinine clearance requirements differ for a specific study drug or drug combination, these criteria are described in the relevant module.

- **5.2.1.3 Consent based on biomarker status:** Addition of *BRAF, MET* and *RET* as exclusion biomarkers with explanation that cohort allocation will not be delayed to determine *ROS1, BRAF, MET or RET* status, for patients harbouring a HUDSON inclusion marker based on pre-existing molecular test data.

5.3 Lifestyle restrictions: Revised to ensure consistency in reproduction and contraception requirements across each module. Patients will be required to adopt birth control methods (and avoid the donation of sperm) from screening until 6 months after the last dose of study drug. The reproduction and contraception requirements described in the core protocol are applicable to each module in the study.

7.1 Discontinuation of study treatment: Updated in line with the new durvalumab IB Edition 12.

7.3 Withdrawal from the study:

- Added that patients assigned to a cohort, for whom one or more of the exclusion biomarkers are detected for the first time during retrospective confirmation of biomarker status, may be replaced at the discretion of AstraZeneca.

- For consistency, *BRAF*, *MET* and *RET* were included in the list of exclusion biomarkers.

Clarification of CTCAE version to use is v4.03. This was added to section 8.2.1 Clinical safety laboratory assessments, section 9.4.6 Safety analyses and Appendix B6 Intensity rating scale.

Table 5 Laboratory Safety Variables: Serum or plasma phosphate included in core panel of safety monitoring tests and will be monitored in all patients.

8.2.4 Electrocardiograms: Clarification that triplicate ECG measurements are also required at baseline, in addition to on-treatment ECGs.

8.3.4 Adverse event data collection: To align with new internal IO data standards, the following additional information will be captured; changes in CTCAE grade for each AE and the date it changes, whether an AE is of special interest and if AEs are infusion related.

8.5 Pharmacokinetics: Addition of a timeframe for pre-dose PK samples to be taken.

8.7.2 Storage and destruction of genetic samples: Amended to state that genetic analyses will not be reported in the CSR but in peer-reviewed journals.

8.8.1.1 Collection of archival tumour samples: micro-arrays will not be performed as part of the study so were deleted.

The statistical methods have been amended as follows:

- Removal of the word "initial" from "initial analysis of cohort" in sections **1.2 Synopsis, 7.3 Withdrawal from the study** and **9.2 Sample size determination.**
- **1.2 Synopsis** and **9.4.1 Definition of endpoints:** Corrected the definition of ORR endpoint, removing the terminology "best" from overall response rate.
- **9.2 Sample size determination:** Corrected the confidence intervals.
- **9.4.2 General considerations:** Amended to state that the data will be presented separately for each cohort within each module, to allow for the reporting of the results on a per module basis. Also clarified that the efficacy endpoints for the biomarker-matched cohort will be summarised according to their allocated cohort and by their confirmatory central test result.

Appendix A3 Informed consent process: Due to the complexity of HUDSON, text added to exclude patients who are not able to consent themselves.

Appendix D Genetics: Following a request from the Austrian Health Authority, additional information about how the results of genetic analyses will be reported were added.

Appendix E Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law: Additional instructions on how to manage potential Hy's Law cases were included as per durvalumab IB Edition 12. **Appendix F Abbreviations:** Corrected the explanation for SUSAR. **Appendix H Toxicity management guidelines for durvalumab:** updated in line with the new durvalumab IB Edition 12. The requirement for expedited reporting of AESIs has also been clarified. **Various administrative changes.**

Version 1.0, 05 September 2017
Initial creation

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

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1. PROTOCOL SUMMARY

1.1 Schedule of Activities

The Schedule of Activities (SoA) for the pre-screening and screening visits is shown in Table 1 below. For the SoA to be performed during the on-treatment period, please refer to the relevant module.

Please note, additional main screening assessments are required for Module 6; these are detailed in Module 6, Table 1.

Table 1 Schedule of Activities – pre-screening and main screening visits

	Pre-screening	Main screening	Survival follow-up[f]	Notes
Week (relative to C1D1 [or to C0D1 for modules with a Cycle 0 lead-in])	**≥-4**	**≤4 weeks prior to starting treatment**	**Every 3 months**	Pre-screening to be completed prior to the main screening. The maximum duration of the pre-screening period is 6 months.
Day (relative to C1D1 [or to C0D1 for modules with a Cycle 0 lead-in])		≤28 days prior to starting treatment		
Informed consent; pre-screening				Two separate ICFs are required, one each for pre-screening and main screening
Informed consent: access to pre-existing molecular information and/or molecular profile screening, and new biopsy[g]	X			Section 5.2.1
Provision of archival tumour sample for molecular profiling, if available	X			Section 5.2.1, please provide the most recent sample.
Provision of new tumour biopsy (mandatory) for translational research and molecular profiling[a,g,h]	X			Section 5.2.1. The new biopsy must be taken approximately ≤3 months from main screening consent. The new biopsy must be post-progression on prior PD-1/PD-L1 therapy.
Demography (age, gender, race, ethnicity)	X			Section 4.1.4 and Section 5.4
Cancer history including prior anti-cancer treatment	X			Section 4.1.4 and Section 5.4
AE/SAE assessment	X	X[e]		Section 8.3
Informed consent; main screening[b]				Two separate ICFs are required, one each for pre-screening and main screening For additional Module 6 assessments, see Module 6 Table 1
Informed consent: study procedures		X[e]		Section 5.2.1

	Pre-screening	Main screening	Survival follow-up[f]	Notes
Week (relative to C1D1 [or to C0D1 for modules with a Cycle 0 lead-in])	**≥-4**	**≤4 weeks prior to starting treatment**	**Every 3 months**	Pre-screening to be completed prior to the main screening. The maximum duration of the pre-screening period is 6 months.
Day (relative to C1D1 [or to C0D1 for modules with a Cycle 0 lead-in])		≤28 days prior to starting treatment		
Consent for genetic sample and analysis (optional)		X		Section 8.7 and Appendix D
Study procedures				For additional Module 6 main screening assessments, see Module 6 Table 1
Medical history, including tobacco use		X		Section 4.1.4 and Section 5.4
Physical examination (complete)		X[e]		Section 8.2.2
Vital signs		X[e]		Section 8.2.3
ECG		X[e]		Section 8.2.4
WHO/ECOG performance status		X[e]		Section 8.2.5
Concomitant medications		X[e]		See relevant module
Eligibility criteria		X[e]		Sections 5.1 and 5.2
Laboratory assessments				For additional Module 6 main screening assessments, see Module 6 Table 1
Clinical chemistry		X[e]		Section 8.2.1.
Haematology		X[e]		Section 8.2.1.

	Pre-screening	Main screening	Survival follow-up[f]	Notes
Week (relative to C1D1 [or to C0D1 for modules with a Cycle 0 lead-in])	**≥-4**	**≤4 weeks prior to starting treatment**	**Every 3 months**	Pre-screening to be completed prior to the main screening. The maximum duration of the pre-screening period is 6 months.
Day (relative to C1D1 [or to C0D1 for modules with a Cycle 0 lead-in])		≤28 days prior to starting treatment		
APTT and INR		X[e]		Section 8.2.1.
TSH, free T_3, and free T_4		X[e]		Free T_3 and free T_4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system
Urinalysis		X[e]		Section 8.2.1.
Hepatitis B and C and HIV		X		Sections 5.2 and 8.2.1.2. Tests performed ≤6 weeks prior to starting treatment are acceptable if the additional 2-week window is agreed with the study physician
Pregnancy test		X[e]		Section 8.2.1.2. For women of childbearing potential only
Blood for CCI assessments (tracking of tumour molecular aberrations in the circulation)		X		Section 8.8.2
Blood for CCI (diagnostic development and molecular profiling[d])	X			Section 8.8.2
Genetic sample (optional DNA element for long-term storage/future use)[c]		X		Section 8.7
Whole blood sample for CCI		X		Section 8.8.3
Tumour evaluation (CT or MRI) (RECIST 1.1)		X		Section 8.1.1 This will include a brain CT or MRI scan.
Subsequent cancer therapy (screen fail patients)[f]			X	Section 8.1.3.2 Every 3 months.

	Pre-screening	Main screening	Survival follow-up[f]	Notes
Week (relative to C1D1 [or to C0D1 for modules with a Cycle 0 lead-in])	**≥-4**	**≤4 weeks prior to starting treatment**	**Every 3 months**	Pre-screening to be completed prior to the main screening. The maximum duration of the pre-screening period is 6 months.
Day (relative to C1D1 [or to C0D1 for modules with a Cycle 0 lead-in])		≤28 days prior to starting treatment		
Survival status (screen fail patients)[f]			X[f]	Section 8.1.3.2 Every 3 months.

[a] Every effort should be made to collect the new biopsy during pre-screening. The new biopsy may be taken during the main-screen if for any reason it cannot be obtained during pre-screening. See also footnote g specific to Modules 10 and 11.

[b] Every effort should be made to minimise the time between allocation to treatment cohort and starting treatment.

[c] If not taken at screening the sample may be taken at any visit until the final study visit

[d] This may be used for molecular profiling following the availability of a well-validated plasma NGS panel. The timing of blood sample collection in pre-screening for central laboratory molecular profiling, in relation to patient status on immediate prior therapy, will be clarified in the Pathology and Genomics Testing Manual.

[e] Patients in Modules 1 to 5 who are considered for re-allocation should be re-consented and re-screened with the following: physical examination, vital signs, ECG, WHO/ECOG performance status, concomitant medications, eligibility criteria, and laboratory assessments. Screening results obtained >28 days before the first dose of re-allocated therapy should be discussed with the study physician. Note: From implementation of protocol v10.0, optional treatment re-allocation of patients is no longer applicable.

[f] Ad hoc collection of survival status for screen fail patients may be requested for overall survival analyses. Note: Collection of survival follow-up data for screen fail patients is no longer required after implementation of protocol v10.0.

[g] Module 10 and Module 11 only: Patients may be exempt from requiring a new tumour biopsy during pre-screening in agreement with the sponsor study physician, if a tumour sample is obtained after progression on prior anti-PD-(L)1 therapy and ≤ 3 months prior to pre-screening. Where no such sample is available, a tumour sample taken within the previous 24 months is acceptable**.**

[h] On-treatment biopsies are not required if a fresh tumour sample is not collected at pre-screening.

Note, if main screening assessments have been performed within 3 days prior to C1D1, or to C0D1 for modules with a Cycle 0 lead-in, then assessments do not need to be performed on C1D1 or C0D1 pre-dose. If the results of the clinical chemistry, haematology and/or ECG are clinically significant (as determined by the investigator), the tests may need to be repeated and clinical significance confirmed on C1D1 or C0D1 pre-dose. Similarly, if the patient's clinical status has changed, experiences new symptoms or has abnormal vital signs, the patient needs to be assessed by the investigator or designee on C1D1 or C0D1 pre-dose.

AE adverse event; APTT activated partial thromboplastin time; C cycle; CT computed tomography; CCI D day; ECG electrocardiogram; ECOG Eastern Cooperative Oncology Group; HIV human immunodeficiency virus; ICF informed consent form; INR international normalised ratio; MRI magnetic resonance imaging; NGS next generation sequencing; CCI PD-1 programmed cell death protein 1; PD-L1 programmed cell death ligand 1; RECIST Response Evaluation Criteria in Solid Tumours; SAE serious adverse event; TSH thyroid-stimulating hormone; T_3 triiodothyronine; T_4 thyroxine; WHO World Health Organization

1.2 Synopsis

International co-ordinating investigator

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Protocol Title:

An Open-Label, Multi-Drug, Biomarker-Directed, Multi-Centre Phase II Umbrella Study in Patients with Non-Small Cell Lung Cancer, who Progressed on an anti-PD-1/PD-L1 Containing Therapy (HUDSON).

Short Title:

Phase II umbrella study of novel anti-cancer agents in patients with NSCLC who progressed on an anti-PD-1/PD-L1 containing therapy.

Rationale:

Despite the improvement in clinical outcomes with immune checkpoint inhibitors in first- or second-line non-small cell lung cancer (NSCLC) patients, it is becoming increasingly clear that there is a new and significant patient population emerging that does not respond to anti-programmed cell death-1/programmed cell death-ligand 1 (anti-PD-1/PD-L1) containing therapy (primary resistance) or progresses during anti-PD-1/PD-L1 containing therapy (acquired resistance). Following immune checkpoint inhibitor failure, treatment options include chemotherapy and investigative clinical trials, though chemotherapy could be considered the de facto standard of care, in particular docetaxel for patients who have already received platinum-doublet therapy. The limited clinical activity and the toxicity with docetaxel may limit the patient population that can be treated with docetaxel and therefore, novel treatments for these patients are urgently needed. In this Phase II umbrella study, several new treatments will be investigated in molecularly matched and non-matched patient populations after failure of immune checkpoint inhibitors and in the molecular aberration independent patient population.

Objectives and Endpoints

Primary objective:	**Endpoint/variable:**
To obtain an assessment of the efficacy of each treatment by evaluation of objective response rate	Endpoint based on Response Evaluation Criteria in Solid Tumours (RECIST 1.1) Objective response rate (ORR)
Secondary objective:	**Endpoint/variable:**
To assess the efficacy of each therapy by evaluation of tumour response (Disease control rate, Best percentage change in tumour size, Duration of response, Progression free survival) and Overall Survival	Overall Survival (OS) Endpoints based on RECIST 1.1 including: Disease control rate (DCR) Best percentage change in tumour size Duration of response (DoR) Progression free survival (PFS)
Safety objective:	**Endpoint/variable:**
To assess the safety and tolerability of each treatment	Physical examinations, laboratory findings, vital signs, and other safety assessments as specified AEs/SAEs collected throughout the study, from informed consent until the safety follow-up visit
Exploratory objectives:	**Endpoint/variable:**
To investigate changes in tumour burden CCI [redacted] levels in plasma	Collection of plasma samples to include, but not limited to, extraction of CCI [redacted] for investigation of blood-borne cancer biomarkers. Mutant Allelic Fraction (MAF) will be measured in pre-dose and serial (post-dose) plasma samples. The results of this exploratory biomarker research will not form part of the CSR.
To investigate cancer-relevant immune status	Exploratory biomarker analyses of blood and tissue samples, or utilisation of residual samples, for the analysis of tumoral and peripheral biomarkers, may include (but are not limited to) the presence of or changes in levels of RNA, DNA; epigenetic or mutational profiles or signatures; gene or protein expression profiles (eg, PD-L1, B2M, MHC-I, MHC-II); and the number, phenotype, and expression profile of immune cells. The results of this exploratory biomarker research will not form part of the CSR.

Objectives and Endpoints

To quantify CCI [redacted] with the aim of characterising CCI [redacted]	To study therapeutic response/resistance using radiomic analyses of non-invasive medical images extracted from tumour evaluation images (where available) of each measurable lesion to obtain lesion phenotype dynamics in complement to CCI [redacted] dynamics. The results of this exploratory research will not form part of the CSR.
To investigate changes in cancer-related gene mutations and aberrations	Relationship between genomic and genetic aberrations and response based on molecular profile of archival tumour biopsy (where available), pre-dose biopsies, tissue biopsies taken during treatment or at disease progression, and liquid biopsies. The results of this exploratory biomarker research will not form part of the CSR.
To collect and store DNA, derived from a blood sample, for future exploratory research into genes/genetic factors that may influence response eg, distribution, safety, tolerability and efficacy of study treatments (optional)	Correlation of polymorphisms with variations in safety or response parameters to study drugs. The results of this exploratory biomarker research will not form part of the CSR.
To investigate outcomes in patients who screen fail[a]	Overall survival will be presented and subsequent anti-cancer therapies will be summarised, to support the interpretation of outcomes for treatment interventions. Patients will be grouped by cancer-related molecular changes as determined by tissue or plasma CCI [redacted] results.
To assess the PK of AZD9150 (Module 2), the PK of durvalumab and AZD6738 (Module 10), the PK of trastuzumab deruxtecan and durvalumab (Module 6), and the PK of cediranib (Module 7)	Concentration of AZD9150, AZD6738, trastuzumab deruxtecan, durvalumab, and cediranib in blood will be summarised, as data allow (sparse sampling)
To investigate the immunogenicity of durvalumab, AZD9150, and trastuzumab deruxtecan	Presence of ADAs for durvalumab, AZD9150, and trastuzumab deruxtecan (confirmatory results: positive or negative)
To collect and store blood and tissue samples for future exploratory research into markers that may correlate with clinical benefit and tolerability.	Correlation of markers with variations in safety or response parameters to study drugs. The results of the exploratory research will not be reported in the CSR. In addition, exploratory work will be conducted to understand, among others, CCI [redacted]
To investigate the emergence of new lesions	New lesions based on standard disease assessment.
To investigate the usage of subsequent anti-cancer therapy	Subsequent anti-cancer therapy

[a] From protocol v10.0 implementation, collection of survival follow-up data for screen failures is no longer required as sufficient data have now been collected to investigate the outcome in patients who screen fail.

Note: per IB, AZD9150 is also known as danvatirsen; per IB, AZD6738 is also known as ceralasertib.

ADA anti-drug antibodies; AE adverse event; B2M beta-2 microglobulin; CSR clinical study report; CCI [redacted] DCR disease control rate; DNA deoxyribonucleic acid; DoR Duration of response; CCI [redacted] MAF Mutant Allelic Fraction; MHC-I/II major histocompatibility class I/II; ORR objective response rate; OS overall survival; PD-L1 programmed cell death ligand 1; PFS progression free survival; PK pharmacokinetics; RECIST Response Evaluation Criteria in Solid Tumours; RNA ribonucleic acid; SAE serious adverse event.

Overall design:

This is an open-label, multi-centre, umbrella Phase II study in patients who have received an anti-PD-1/PD-L1 containing therapy and a platinum-doublet regimen for locally advanced or metastatic NSCLC either separately or in combination. The patient must have had disease progression on a prior line of anti-PD-1/PD-L1 therapy. This study is modular in design, allowing initial assessment of the efficacy, safety, and tolerability of multiple treatment arms.

Within each module, there will be treatment cohorts. Allocation to a treatment cohort will be by analysis of tumour molecular profile to a biomarker-matched group (Group A), a biomarker non-matched group (Group B) or to a molecular aberration independent group (Group C). Within Group B (biomarker non-matched), cohorts will be stratified into patients who are primary resistant (patients who had anti-PD-1/PD-L1 containing therapy but had progression of disease (PD) within ≤24 weeks from the start of that treatment) or developed acquired resistance while on immunotherapy (patients who had PD >24 weeks from the start of anti-PD-1/PD-L1 containing treatment whilst still on that treatment). Within Group C, allocation to cohorts will be independent of patient molecular aberration status.

Study Period:

Date of first patient enrolled: Q4 2017

Estimated date of last patient completed: Q3 2024

Number of Patients:

Biomarker matched and non-matched cohorts (Group A and Group B)

Per protocol version 9.0, there will be approximately 20 evaluable patients in each treatment cohort, with the option to expand a cohort to include approximately 20 more patients should an efficacy signal be observed. Alternatively, patients could be enrolled to a non-comparative randomised expansion where approximately an additional 40 patients could be randomised to either study treatment or standard of care/treatment of physician's choice (to be determined and defined in the resulting amendment).

Per protocol version 10.0, the biomarker non-matched cohorts in Module 3 (B.3.ACQ and B.3.PRI) were each further expanded to include up to approximately 30 more patients (to a total of up to approximately 50 patients per biomarker non-matched cohort). Recruitment to Cohort A.3.ATM was also re-opened and expanded per protocol version 10.0, to an

approximate total of 40 patients. As per protocol version 12.0, all three cohorts in Module 3 have been closed for enrolment.

For Module 9 (closed to recruitment), enrolment of an expanded cohort of approximately 40 evaluable patients was planned. This was based on encouraging preliminary data from Module 3. Data were to be reviewed after the first 20 patients in each treatment cohort and continue up to approximately 40 evaluable patients unless the emerging data review indicated a less than expected efficacy signal. Enrolment continued during the review of the data.

Following a regular data review (data cut-off 26 October 2021), the decision was made by AstraZeneca to close recruitment to Module 9 (both Cohorts CCI), and to re-open and expand Module 3 (Cohorts CCI), as described above.

Molecular aberration independent cohorts (Group C)

Per protocol version 10, Module 10 (in Group C) is included in this study. Introduction of Module 10 follows CCI to gather additional data on the impact of different doses of AZD6738 to support a CCI therefore, the study decision framework does not apply to this module. After the screening visits and confirmation of eligibility, a total of up to approximately C patients (up to approximately C patients per cohort), independent of their molecular aberration status, will be randomly allocated in a 2:1 ratio to receive 1 of the following 2 doses of AZD6738 in combination with durvalumab:

- AZD6738 160 mg BD
- AZD6738 240 mg BD

Per protocol version 11, Module 11 (in Group C) is included in this study. Introduction of Module 11 is to further investigate CCI as it is considered to be CCI
After the screening visits and confirmation of eligibility, a total of up to approximately 40 patients, independent of their molecular aberration status, may be enrolled to receive AZD6738 240 mg BD monotherapy.

Treatments and treatment duration:

This protocol has a modular design, with the potential for future treatment arms to be added via protocol amendment. This protocol refers to the following modules and study drugs. For specific information on each of the study drugs, please refer to the relevant module. (Note: As of protocol version 13.0, all modules are closed to recruitment).

- Module 1 (Appendix I): Durvalumab in combination with olaparib (AZD2281). This applies to Group A (biomarker matched) and Group B (biomarker non-matched).

- Module 2 (Appendix J): Durvalumab in combination with AZD9150 (Note: per Investigator's brochure [IB], AZD9150 is also known as danvatirsen). This applies to Group B (biomarker non-matched).
- Module 3 (Appendix K): Durvalumab in combination with AZD6738 (ceralasertib). (AZD6738 dosed for 7 days as monotherapy prior to cycle 1, and then for 7 days [from Days 22 to 28] in every 4-week combination cycle). This applies to Group A (biomarker matched) and Group B (biomarker non-matched).
- Module 4 (Appendix L): Durvalumab in combination with vistusertib (AZD2014). This applies to Group A (biomarker matched).
- Module 5 (Appendix M): Durvalumab in combination with oleclumab (MEDI9447). This applies to Group A (biomarker matched) and Group B (biomarker non-matched).
- Module 6 (Appendix N): Durvalumab in combination with trastuzumab deruxtecan (DS-8201a). This applies to Group A (biomarker matched).
- Module 7 (Appendix O): Durvalumab in combination with cediranib (AZD2171). This applies to Group B (biomarker non-matched).
- Module 8 (Appendix P): AZD6738 (ceralasertib) monotherapy (AZD6738 dosed for 14 days [from Days 1 to 14] in every 4-week cycle). This applies to Group A (biomarker matched).
- Module 9 (Appendix Q): Durvalumab in combination with AZD6738 (ceralasertib) (AZD6738 dosed for 14 days [from Days 15 to 28] in every 4-week combination cycle). This applies to Group B (biomarker non-matched).
- Module 10 (Appendix R): Durvalumab in combination with AZD6738 (ceralasertib). (AZD6738 dosed for 7 days as monotherapy prior to cycle 1, and then for 7 days [from Days 22 to 28] in every 4-week combination cycle at starting doses of 160 mg and 240 mg). This applies to Group C (molecular aberration independent).
- Module 11 (Appendix S): AZD6738 (ceralasertib) monotherapy (AZD6738 dosed for 7 days at 240 mg [from Days 1 to 7] in every 4-week cycle). This applies to Group C (molecular aberration independent).

Enrolment to Group C molecular aberration independent cohorts (Module 10 and Module 11) will be prioritised over other cohorts and will be sequential such that recruitment to Module 11 will be prioritised once Module 10 enrolment is complete.

Eligible patients will be enrolled concurrently into the biomarker-matched cohorts (see Figure 4). Enrolment to the biomarker non-matched cohorts will be sequential (see Section 4.1.3). Patients who meet core protocol eligibility criteria but do not meet module-specific eligibility criteria of the module they have been allocated to, based on their biomarker result, may be allocated to a subsequent available Module. Once approximately 20 patients have been allocated to the first primary or acquired resistant cohort, patients will be allocated to a subsequent primary or acquired resistant cohort. Patients that have been allocated but are unable to proceed to main screening and treatment will be replaced to ensure approximately 20 patients are dosed in each cohort.

Statistical methods

Sample size

Biomarker matched and non-matched cohorts (Group A and Group B)

The primary efficacy endpoint is objective response rate (ORR), and this endpoint will be used to define the sample size.

An analysis will be performed after approximately the CCI evaluable patient in a cohort, or the final patient dosed in a cohort if enrolment ended early, has had the opportunity for 2 on-treatment RECIST scans or has discontinued or withdrawn from treatment. The analysis will provide CCI and will also give a reasonable chance of detecting any CCI in each cohort, should one exist.

If the true ORR is equal to CCI then there is a CCI probability to see 4 or more responses out of C patients. Also, there is only a CCI to see CCI responses out of C patients if the true ORR is CCI.

Per protocol version 9.0, if an efficacy signal is demonstrated within a cohort, such as CCI observed confirmed complete responses (CR) or confirmed partial responses (PR) the cohort may be expanded. This may be to expand the size of a cohort to include approximately 20 more patients. Alternatively, patients could be enrolled to a non-comparative randomised expansion where approximately an additional 40 patients will be randomised to study treatment or standard or care/treatment of physician's choice. If a non-comparative randomised expansion is proposed, a protocol amendment will be provided.

Per protocol version 10.0, the biomarker non-matched cohorts in Module 3 (B.3.ACQ and B.3.PRI) were each further expanded to include up to approximately 30 more patients (to a total of up to approximately 50 patients per cohort; Cohort A.3.ATM was also expanded to an approximate total of 40 patients. As per protocol version 12.0, all three cohorts in Module 3 have been closed for enrolment.

Molecular aberration independent cohorts (Group C)

For Module 10, a total of up to approximately C patients may be enrolled. Each cohort in Module 10 will explore a different dose of AZD6738 in combination with durvalumab: 160 mg BD and 240 mg BD (Cohort C.10.160 and Cohort C.10.240, respectively). An CCI will be performed CCI following approximately CCI in the 160 mg cohort and approximately CCI in the 240 mg cohort first dose, or when approximately CCI in the 160 mg cohort and approximately CCI in the 240 mg cohort have discontinued or withdrawn from treatment. No statistical tests will be performed; all analyses will be descriptive. Further details will be provided in the SAP.

For Module 11, a total of up to approximately 40 patients may be enrolled. A futility analysis will be carried out after approximately the CCI evaluable patient in the cohort has had the opportunity for 2 on-treatment RECIST assessments or has discontinued or withdrawn from treatment. If the futility criteria are not met (>0 confirmed responses out of the C patients), the cohort will be expanded and a second interim analysis will be carried out after the CCI evaluable patient in the cohort, or the final patient dosed in the cohort if enrolment has ended early, has had the opportunity for 2 on-treatment RECIST assessments, or has discontinued or withdrawn from treatment. There is the potential option to expand the cohort to 40 patients, should an efficacy signal, such as C or more confirmed responses out of the 23 patients, be observed, and supported by emerging data (including progressive disease rate, discontinuation rate and death rate). The interim analysis will provide CCI data and will also CCI in this cohort, should one exist.

This decision framework is a recommendation only and any decision to stop or expand at any time will be at the discretion of the sponsor and will be based on emerging efficacy, safety and tolerability data.

Outcome measures for analysis

The primary efficacy variable for this study is ORR. The ORR is defined as the percentage of patients who have an objective response of confirmed CR or confirmed PR.

Other efficacy endpoints include disease control rate (DCR), best percentage change from pre-dose in tumour size, duration of response (DoR), progression free survival (PFS) and overall survival (OS).

All tumour assessment-related endpoints will be based on RECIST 1.1.

Methods for statistical analysis

Data will be presented separately for each cohort within each module.

For each biomarker-matched cohort, the efficacy endpoints will be summarised for all patients and by their central test result. However, in certain circumstances (eg, if central test result not available) and as described in SAP, local biomarker test results may be used.

For each non-matched cohort, the efficacy endpoints will be summarised by the investigator-assigned response (primary or acquired resistance) to prior PD-1/PD-L1 therapy.

For patients in Module 10 of Group C, data will be summarised by dose group and by resistance type; primary or acquired resistance to prior PD-1/PDL-1 therapy. Data for all patients in Module 11 of Group C will be summarised together. Additional subgroup analyses may be performed and will be specified in the SAP.

Tumour response based upon RECIST 1.1 will be used to summarise ORR (Clopper-Pearson 80% confidence interval will be calculated), DCR, best percentage change from pre-dose in tumour size, DoR and PFS. Kaplan-Meier plots will be produced if appropriate for DoR, PFS and OS.

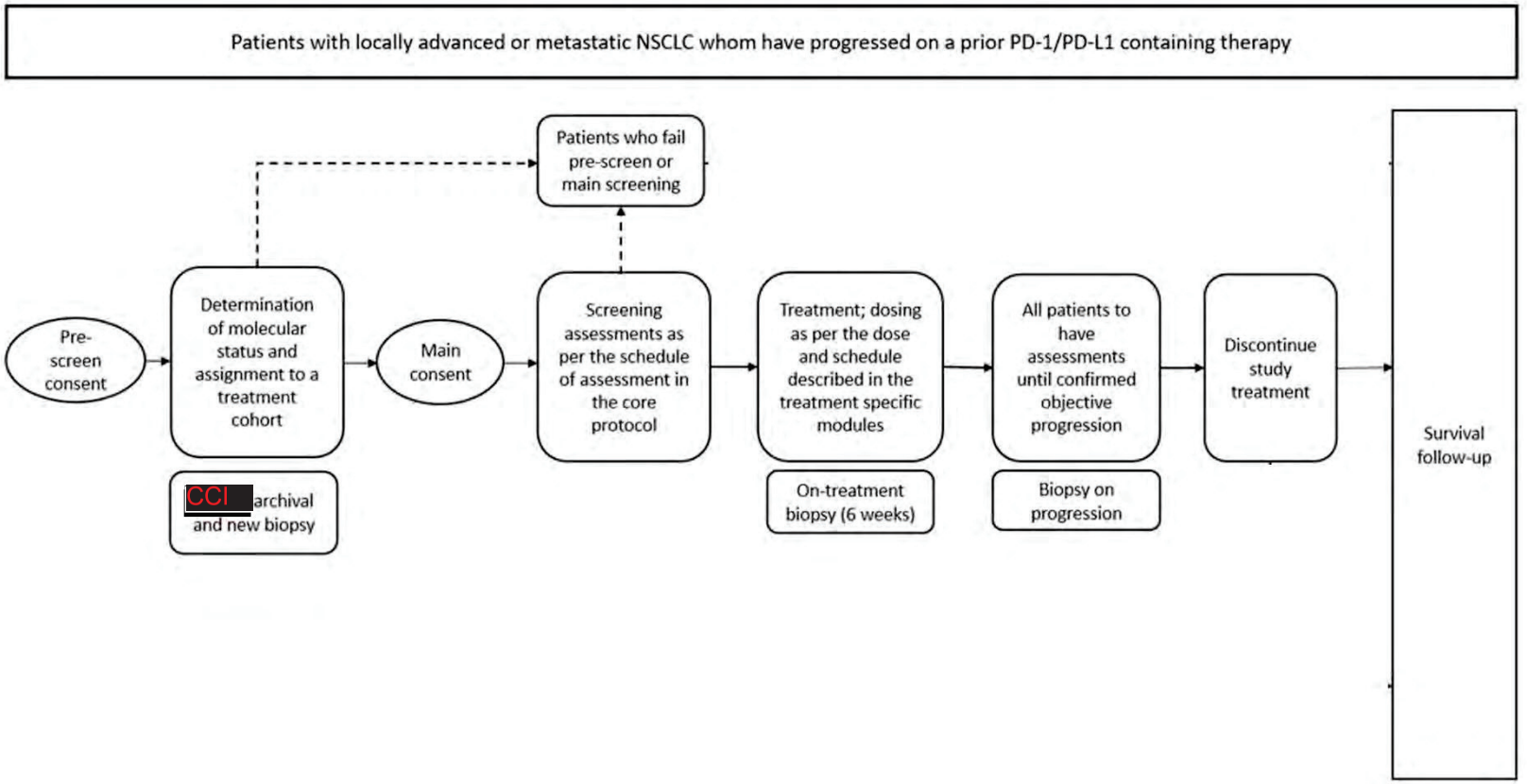
Safety and tolerability will be assessed in terms of adverse events (AEs), deaths, laboratory data, vital signs and electrocardiograms (ECGs). These will be collected for all patients. Appropriate descriptive summaries of these data will be presented.

Details of analyses will be provided in the Statistical Analysis Plan (SAP).

1.3 Schema

The general study design is summarised in Figure 1.

Figure 1 Study design



From implementation of protocol v11.0, enrolment to Group C molecular aberration independent cohorts (Module 10 and Module 11) will be prioritised and be sequential, such that recruitment to Module 11 will be prioritised once Module 10 enrolment is complete.
For additional screening assessments in Module 6, see the module.
CCI NSCLC, non-small cell lung cancer; PD-1, programmed cell death-1; PD-L1, programmed cell death ligand 1.

2. INTRODUCTION

2.1 Study rationale

This is an open-label, multi-centre, umbrella Phase II study in patients who have received anti-programmed cell death-1/anti-programmed cell death ligand 1 (anti-PD-1/PD-L1) containing therapy and a platinum-doublet regimen for locally advanced or metastatic NSCLC either separately or in combination. The patient must have had disease progression on a prior line of anti-PD-1/PD-L1 therapy. This study is modular in design, allowing initial assessment of the efficacy, safety, and tolerability of multiple treatment arms. There is currently no established therapy for patients who have developed resistance to PD-1/PD-L1 and platinum-doublet therapies, and novel treatments are urgently needed.

At the outset, this study will explore a series of investigational treatment options in different biomarker-matched cohorts (Group A), biomarker non-matched cohorts (Group B), and as of implementation of protocol version 10.0, molecular aberration independent cohorts (Group C). This study has the potential to include new study drugs in the future. If an additional cohort is deemed necessary, a protocol amendment will be provided (see Section 4.1.5).

2.2 Background

Lung cancer is the most common cancer worldwide; 85% being NSCLC. It is the most common cause of death from cancer with 1.6 million deaths or 19.4% of total cancer deaths attributed to this disease (Gridelli et al 2015). At least 70% of cases present late with inoperable Stage III or metastatic Stage IV disease. In some Stage III cases chemoradiotherapy plus/minus surgery can provide long-term control while nearly all patients with Stage IV disease are incurable and treated with palliative systemic medical treatment.

Advances over the past 20 years have seen histological and molecular classification of NSCLC so that squamous and non-squamous carcinomas are clearly distinguishable from each other and subdivision based on molecular aberrations is now possible (Hirsch et al 2016). Whilst some of these molecular segments have approved therapies, including patients with epidermal growth factor receptor (*EGFR*)-activating and resistance mutations and anaplastic lymphoma kinase (*ALK*) translocations and *ROS1* aberrations amongst others, more than 50% of adenocarcinomas and more than 95% of squamous cell carcinomas do not, especially in the relapsed setting.

Until recently, platinum-based combination chemotherapy was the standard of care for first-line therapy in non-squamous and squamous cell carcinoma (NCCN 2017). More recently, checkpoint inhibitors were found to be more efficacious and better tolerated than first-line platinum-based chemotherapy in patients with high PD-L1 expression (see below). Therefore, the treatment landscape has changed and first-line treatment choices are now predominantly based on the PD-L1 expression status and the potential occurrence of

targetable molecular alterations. For example, in *EGFR*- and *ALK*-mutant tumours, tyrosine kinase inhibitors (TKI) such as gefitinib, erlotinib, afatinib, alectinib, ceritinib, and crizotinib are the respective agents of choice in the previously untreated setting. Crizotinib is also approved in some territories for patients with *ROS1* aberrations (Shaw et al 2014).

Immunotherapy with anti-PD-1 or anti-PD-L1 checkpoint inhibitors was first investigated in the Phase I study of nivolumab reported in 2012 (Topalian et al 2012). NSCLC patients included in this trial showed responses, some of which were durable. Subsequent trials of nivolumab and other agents, eg, pembrolizumab and atezolizumab (Brahmer et al 2015, Borghaei et al 2015; Herbst et al 2016), have confirmed responses and improved survival outcomes compared with docetaxel chemotherapy in the second-line treatment setting. The benefit is seen across adenocarcinoma and squamous carcinoma histologies but there are poorer outcomes in *EGFR* and *ALK*-mutant tumours, possibly related to a lower mutational tumour burden and a poorer immune infiltrate in these tumours (Peters et al 2017).

Across the 3 immune checkpoint agents tested in the second-line setting after chemotherapy, nivolumab, pembrolizumab and atezolizumab all show ~20% response rates some of which are durable beyond 18 months. Improved median OS in the range of 9 to 12 months in nivolumab treated patients compared to 6 to 9 months in docetaxel treated patients was seen in the pivotal checkmate 017 and 057 trials respectively (Brahmer et al 2015, Borghaei et al 2015). In pembrolizumab treated patients on the Keynote 010 trial there was an improved median OS of 14.9 months in the 2 mg/kg treatment arm, a 17.3 months median OS in the 10 mg/kg arm compared with an 8.2 months median OS in docetaxel treated patients (Herbst et al 2016). The Phase III OAK study compared atezolizumab to docetaxel and showed a median OS of 13.8 months for atezolizumab treated patients compared to 9.6 months in the docetaxel arm (Rittmeyer et al 2017). All of these trials were in the platinum-resistant setting and recruited patients regardless of mutation status. However, the Keynote 010 trial was the only trial to prospectively select patients with PD-L1 staining of ≥1%. Stratification for the pembrolizumab and docetaxel arms was then performed for PD-L1≥50% versus 1 to 49%. Pembrolizumab is therefore approved for patients post-chemotherapy with PD-L1 staining in tumour cells of ≥1%, whilst nivolumab and atezoluzimab are approved in all patients irrespective of PD-L1 status.

Patients with cerebral metastases were initially excluded from treatment with anti-PD-1/PD-L1 agents but were then allowed to enrol if their cerebral disease was stable. A pooled analysis of 1452 atezolizumab treated patients (enrolled onto OAK, POPLAR, FIR, BIRCH, and PCD4849) with stable treated brain metastases demonstrated significant activity in patients with treated and stable brain metastases (Lukas et al 2017). Outcomes in these patients were superior to docetaxel treated patients with median OS of 20.1 months in the atezolizumab arm versus 11.9 months median OS with docetaxel therapy. The incidence of new brain metastases was also lower in the atezolizumab treated patients.

Efforts to move these agents into the first-line pre-chemotherapy setting have had differing degrees of success: the Phase III checkmate 026 study of upfront nivolumab in Stage IV or recurrent disease recruited patients with ≥1% PD-L1 expression, no *EGFR/ALK* mutations and adequately treated cerebral metastases (if present). The control arm was (histology appropriate) chemotherapy. There was no difference in median PFS or OS outcomes between the arms (Carbone et al 2017). In contrast, the Keynote 024 Phase III study recruited *EGFR/ALK* non-mutant patients with treated brain metastases and tumours with PD-L1 ≥50% positivity (Reck et al 2016). There was a 45% overall response rate in the pembrolizumab arm and median PFS of 10.3 months compared to 6 months and an estimated OS at 1 year of 70% compared to 54% for the chemotherapy arm. Pembrolizumab was therefore approved for patients with PDL1-staining in tumour cells >50% who have had no prior systemic chemotherapy for metastatic NSCLC. Median OS was not reached in either arm at the time of reporting. Crossover was 44% from the chemotherapy to the anti-PD-1/PD-L1 arm.

The randomised Phase II Keynote 021 trial recruited patients irrespective of PD-L1 status but of non-squamous histology and who were *EGFR/ALK* negative (Langer et al 2016). Patients were randomised 1:1 to chemotherapy alone or chemotherapy (as per standard of care) plus pembrolizumab (for 2 years). Progression free survival was superior in the experimental arm with 13 months compared to 8.9 months but there was no difference in OS (Langer et al 2016). Taken together there is significant activity of PD-1/PD-L1 agents in NSCLC in both the second-line and first-line settings (Peters et al 2017), although the optimal strategy for patient selection and sequencing of treatments is still an area of active research. Combinations with chemotherapies, and other immunotherapies such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibodies are also being actively evaluated.

Despite the great improvement with these immune checkpoint inhibitors in first- or second-line, it is becoming increasingly clear that there is a new and significant patient population emerging that does not respond to anti-PD-1/anti-PD-L1 containing therapy (primary resistance) or progresses during anti-PD-1/anti-PD-L1 containing therapy (acquired resistance). There is currently no established therapy following immune checkpoint failure though chemotherapy could be considered the de facto standard of care, in particular docetaxel for patients who have already received platinum-doublet therapy. Modest efficacy and toxicity with docetaxel may limit the patient population that can be treated with docetaxel and therefore, novel treatments for these patients are urgently needed. In this Phase II umbrella study, several new combinations will be investigated in molecularly matched and non-matched patient populations after failure of immune checkpoint inhibitors and in the molecular aberration independent patient population.

Molecular matching will involve sequencing DNA from patient samples for the molecular aberrations and immunohistochemical analysis of protein expression listed in Table 2. The table lists the prevalence of each aberration and protein expression. Molecular prevalence data

were derived by calling mutations from The Cancer Genome Atlas, lung adenocarcinoma, and squamous cohorts using the sponsor's internal pipeline. Details of the patient allocation algorithm are contained within the Pathology and Genomic Testing Manual. A summary of the guiding rationale is provided in Section 4.2.3.

Table 2 Molecular aberrations

Gene	Prevalence (%)
BRCA1,2	10
Other HRR	13
ATM^{MUT}	4
ATM^{LOW} (protein/IHC)	8
CCI	12
LKB1 (STK11)	10-15
CD73^{HIGH} (protein/IHC)	21
HER2 expression (protein/IHC)	45
HER2 mutation	2-4[a]

Mazières et al 2013.
ATM Ataxia telangiectasia mutated; *BRCA* breast cancer associated gene; CD cluster of differentiation; HER2 human epidermal growth factor receptor 2; *HRR* homologous recombination repair gene; IHC immunohistochemistry; *LKB1* liver kinase B1 (also known as *STK11*; serine threonine kinase 11); CCI

2.3 Benefit/risk assessment

The emergence of an immune checkpoint inhibitor resistant population of NSCLC patients especially in the third-line setting has resulted in an unmet need. Docetaxel may have a small median OS benefit compared to best supportive care (7 months versus 4.6 months, p=0.047) if the results of the pivotal docetaxel trial in the second-line chemotherapy refractory setting are translatable to this population (Shepherd et al 2000). Docetaxel had similar efficacy compared to pemetrexed in non-squamous NSCLC (Fossella et al 2004) in the pre-immune-checkpoint era.

The mechanisms of resistance to anti-PD-1/PD-L1 agents are the subject of numerous translational studies and it is anticipated that as these are defined, new therapeutic strategies to overcome resistance will be devised. Such strategies may target killing the tumour cell directly, removing immunosuppressive elements in its microenvironment or activating the effector T-cell itself to overcome other immune checkpoints.

The definition of molecular groups within the NSCLC population not currently served by approved therapies could expand the number of active agents available to patients. Such therapies often have favourable toxicity profiles and survival outcomes within their defined populations and could therefore be advantageous over standard of care chemotherapy.

Ultimately defining targetable mutations beyond *EGFR/ALK/ROS1/BRAF/MET* and *RET* will favourably alter treatment paradigms.

Patients recruited to HUDSON will have received an anti-PD-1/PD-L1 containing therapy and a platinum-doublet regimen, and will have progressed on a prior line of anti-PD-1/PD-L1 therapy, and therefore not have treatment options other than standard of care chemotherapy, such as docetaxel, or investigative clinical trials (NCCN 2017). The poor survival outcome and toxicity profile of chemotherapy in this setting means that more efficacious and tolerable therapies are highly desirable and present a potential advantage for these patients.

Although the potential benefits of each agent as monotherapy or in combination in patients with NSCLC are unknown at this time, non-clinical and clinical data to date demonstrate evidence of anti-tumour activity for each agent. The non-clinical safety profile and emerging safety profile from the early clinical studies with each agent have not identified any risks that would preclude investigation in this setting. The study design aims to minimise potential risks, and monitoring is in place for those risks deemed to be most likely or serious. Thus, the benefit/risk assessment for this Phase II study appears acceptable based on the lack of effective alternative treatments, the limited life expectancy due to advanced disease, and the strength of the scientific hypothesis under evaluation.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of individual study drugs may be found in their respective Investigator's Brochures and the relevant modules.

3. OBJECTIVES AND ENDPOINTS

Table 3 Study objectives

Objectives	Endpoint/Variable
Primary objective:	**Endpoint/variable:**
To obtain an assessment of the efficacy of each treatment by evaluation of objective response rate	Endpoint based on Response Evaluation Criteria in Solid Tumours (RECIST 1.1) Objective response rate (ORR)
Secondary objective:	**Endpoint/variable:**
To assess the efficacy of each therapy by evaluation of tumour response (Disease control rate, Best percentage change in tumour size, Duration of response, Progression free survival) and Overall Survival	Overall Survival (OS) Endpoints based on RECIST 1.1 including: • Disease control rate (DCR) • Best percentage change in tumour size • Duration of response (DoR) • Progression free survival (PFS)

Table 3 Study objectives

Objectives	Endpoint/Variable
Safety objective:	**Endpoint/variable:**
To assess the safety and tolerability of each treatment	Physical examinations, laboratory findings, vital signs, and other safety assessments as specified AEs/SAEs collected throughout the study, from informed consent until the safety follow-up visit
Exploratory objectives:	**Endpoint/variable:**
To investigate changes in tumour burden using CCI levels in plasma	Collection of plasma samples to include, but not limited to, extraction of ctDNA for investigation of blood-borne cancer biomarkers. Mutant Allelic Fraction (MAF) will be measured in pre-dose and serial (post-dose) plasma samples. The results of this exploratory biomarker research will not form part of the CSR.
To investigate cancer-relevant immune status	Exploratory biomarker analyses of blood and tissue samples, or utilisation of residual samples, for the analysis of tumoral and peripheral biomarkers, may include (but are not limited to) the presence of or changes in levels of RNA, DNA; epigenetic or mutational profiles or signatures; gene or protein expression profiles (eg, PD-L1, B2M, MHC-I, MHC-II); and the number, phenotype, and expression profile of immune cells. The results of this exploratory biomarker research will not form part of the CSR.
To quantify CCI with the aim of characterising CCI	To study therapeutic response/resistance using radiomic analyses of non-invasive medical images extracted from tumour evaluation images (where available) of each measurable lesion to obtain lesion phenotype dynamics in complement to CCI dynamics. The results of this exploratory research will not form part of the CSR.
To investigate changes in cancer-related gene mutations and aberrations	Relationship between genomic and genetic aberrations and response based on molecular profile of archival tumour biopsy (where available), pre-dose biopsies, tissue biopsies taken during treatment or at disease progression, and liquid biopsies. The results of this exploratory biomarker research will not form part of the CSR.
To collect and CCI derived from a blood sample, for future exploratory research into genes/genetic factors that may influence response eg, distribution, safety, tolerability and efficacy of study treatments (optional)	Correlation of polymorphisms with variations in safety or response parameters to study drugs. The results of this exploratory biomarker research will not form part of the CSR.

Table 3 Study objectives

Objectives	Endpoint/Variable
To investigate outcomes in patients who screen fail[a]	Overall survival will be presented and subsequent anti-cancer therapies will be summarised, to support the interpretation of outcomes for treatment interventions. Patients will be grouped by cancer-related molecular changes as determined by tissue or plasma CCI results.
To assess the PK of AZD9150 (Module 2), the PK of durvalumab and AZD6738 (Module 10), the PK of trastuzumab deruxtecan and durvalumab (Module 6), and the PK of cediranib (Module 7)	Concentration of AZD9150, AZD6738, trastuzumab deruxtecan, durvalumab, and cediranib in blood will be summarised, as data allow (sparse sampling)
To investigate the immunogenicity of durvalumab, AZD9150 and trastuzumab deruxtecan	Presence of ADAs for durvalumab AZD9150 and trastuzumab deruxtecan (confirmatory results: positive or negative)
To collect and store blood and tissue samples for future exploratory research into markers that may correlate with clinical benefit and tolerability.	Correlation of markers with variations in safety or response parameters to study drugs. The results of the exploratory research will not be reported in the CSR. In addition, exploratory work will be conducted to understand, among others, CCI
To investigate the emergence of new lesions	New lesions based on standard disease assessment.
To investigate the usage of subsequent anti-cancer therapy	Subsequent anti-cancer therapy

[a] From protocol v10.0 implementation, collection of survival follow-up data for screen failed patients is no longer required as sufficient data have now been collected to investigate the outcome in patients who screen fail.

Note: per IB, AZD9150 is also known as danvatirsen; per IB, AZD6738 is also known as ceralasertib.
ADA anti-drug antibodies; AE adverse event; B2M beta-2 microglobulin; CSR clinical study report; CCI DCR disease control rate; DNA deoxyribonucleic acid; DoR Duration of response; CCI MAF Mutant Allelic Fraction; MHC-I/II major histocompatibility class I/II; ORR objective response rate; OS overall survival; PD-L1 programmed cell death ligand 1; PFS progression free survival; PK pharmacokinetics; RECIST Response Evaluation Criteria in Solid Tumours; RNA ribonucleic acid; SAE serious adverse event.

4. STUDY DESIGN

4.1 Overall design

This is an open-label, multi-centre, umbrella Phase II study in patients who have received an anti-PD-1/PD-L1 containing therapy and a platinum-doublet regimen for locally advanced or metastatic NSCLC either separately or in combination. The patient must have had disease progression on a prior line of anti-PD-1/PDL1 therapy. This study is modular in design, allowing initial assessment of the efficacy, safety, and tolerability of multiple treatment arms.

For an overview of the study design see Figure 1, Section 1.3. For details on treatments given during the study, see the relevant module.

For details on what is included in the efficacy and safety endpoints, see Section 3 Objectives and Endpoints.

4.1.1 Modular protocol structure

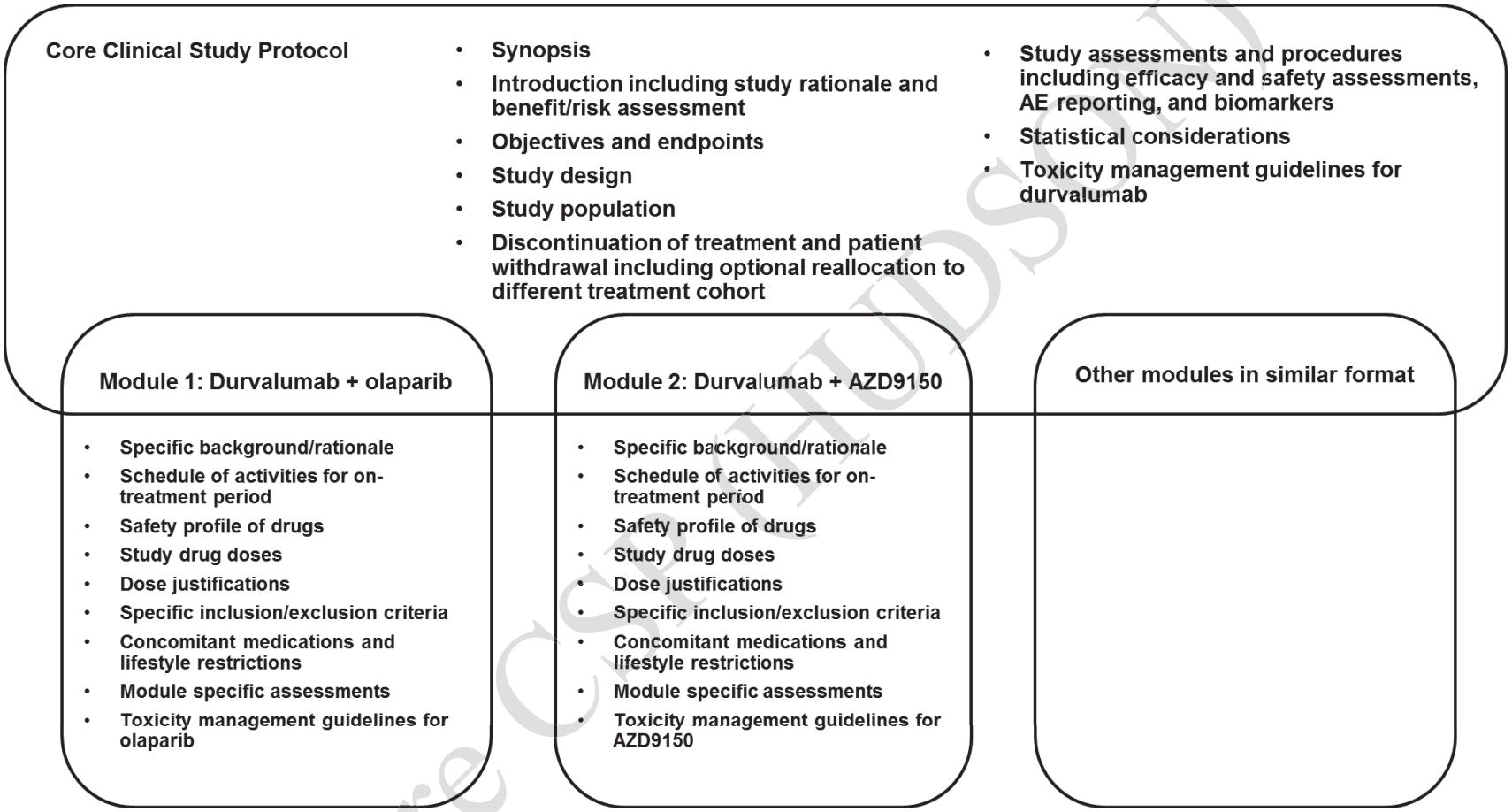
The structure of the protocol will also follow a modular design. Information relating to the overall study, including study objectives, rationale, core inclusion and exclusion criteria, safety assessments, and AE reporting can be found in the core protocol.

Study drug-specific information including doses and justifications, toxicity management, dose modifications and concomitant medications can be found in the relevant module.

Toxicity management guidelines for durvalumab are provided.

The modular protocol structure is shown in Figure 2, and a study flow diagram showing the treatment cohorts is shown in Figure 4.

Figure 2 Modular protocol structure



Note:

- Recruitment to Cohort B.5.PRI is closed per version 7.0 of the protocol and, as a result, will not reach 20 evaluable patients.
- Recruitment to Module 4 is closed per version 3.1 of the protocol and, as a result, Module 4 will not reach 20 evaluable patients.
- Recruitment to Module 8 CCI per version 10.0 of the protocol and, as a result, CCI
- For Module 6 (durvalumab + trastuzumab deruxtecan) see Section 4.1.3.
- Recruitment to Module 9 is closed to recruitment following a regular data review (data cut-off 26 October 2021) and, CCI (see Section 9.2).

Molecular aberration independent cohorts (Group C)

Per protocol version 10, Module 10 in Group C is included in this study. After the screening visits and confirmation of eligibility, a total of up to approximately 80 patients, independent of their molecular aberration status, will be randomly allocated in a 2:1 ratio to receive 1 of the following 2 doses of AZD6738 in combination with durvalumab:

- AZD6738 160 mg BD
- AZD6738 240 mg BD

Each cohort in Module 10 may enrol up to approximately C patients. Introduction of Module 10 follows CCI on CCI of AZD6738 CCI therefore, the study decision framework does not apply to this module.

Per protocol version 11, Module 11 in Group C is included in this study to further investigate CCI as it is considered to be CCI After the screening visits and confirmation of eligibility, a total of up to approximately 40 patients, independent of their molecular aberration status, may be enrolled to receive AZD6738 240 mg BD monotherapy.

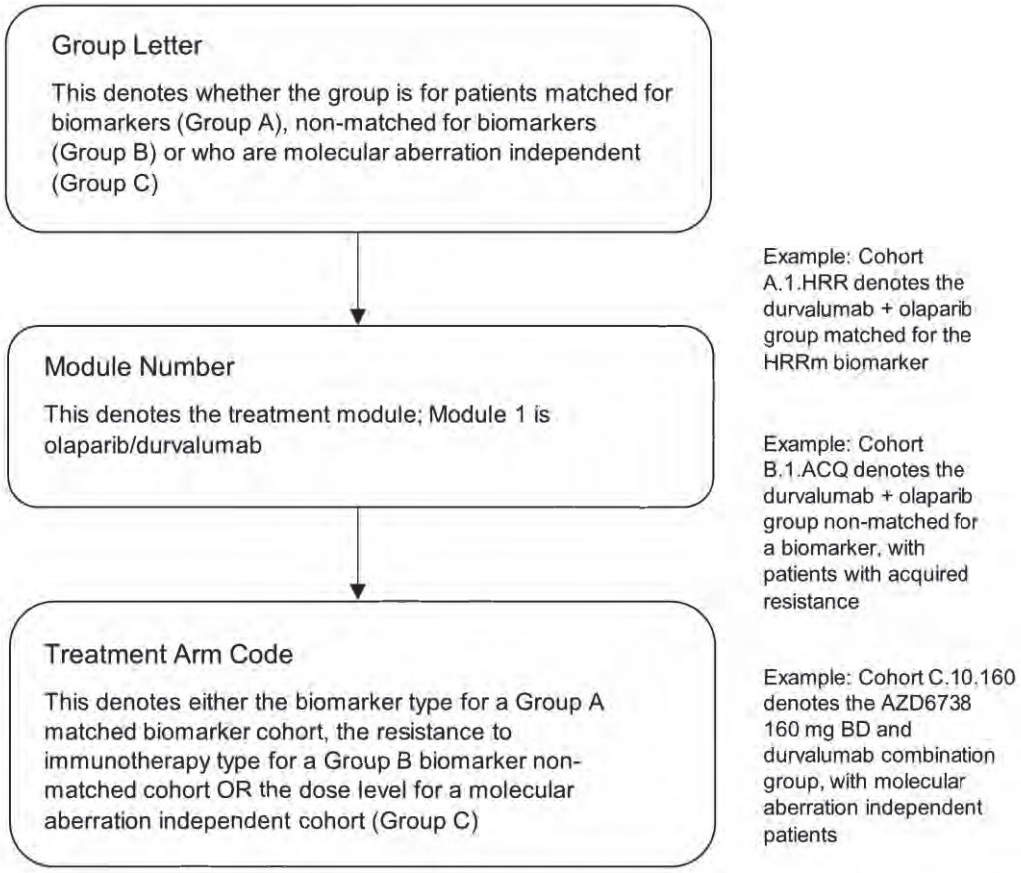
In addition, new treatment cohorts containing additional study drugs may be added in the future via protocol amendment. These study drugs may be administered as monotherapy or in combination. Information on additional treatment groups will be provided in additional modules as appropriate (see Section 4.1.5).

4.1.2 Cohort naming conventions

The study will consist of several study modules, each evaluating the efficacy, safety, and tolerability of specific study drugs or combinations in patients who have locally advanced or

metastatic NSCLC. Allocation to treatment will be by analysis of tumour molecular profile to a biomarker-matched treatment group (Group A), a biomarker non-matched treatment group (Group B) or a molecular aberration independent group (Group C). Within the biomarker non-matched treatment group, patients will be prospectively stratified according to whether they have primary resistance to immunotherapy (eg, Cohort B.1.PRI), or acquired resistance while on immunotherapy (eg, Cohort B.1.ACQ). This will be based on patient response to a prior anti-PD-1/PD-L1 containing therapy. Please refer to Figure 3.

Figure 3 Schematic of the treatment naming conventions



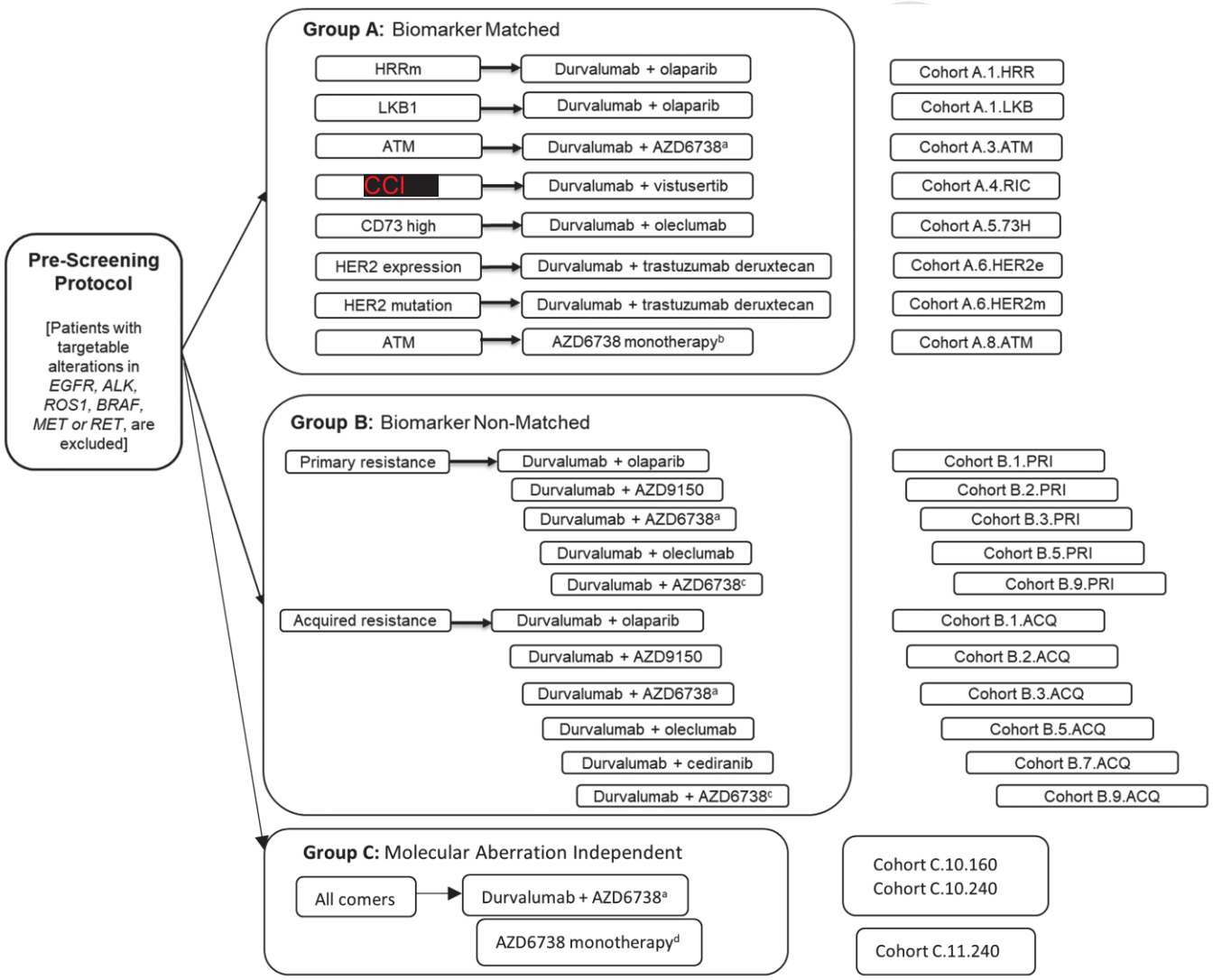
List of modules

The following starting modules for the study are included with this protocol. The structure of the protocol allows for further modules to be added to the core study as required. (Note: As of protocol version 13.0, all modules are closed to recruitment).

- Module 1: Durvalumab + olaparib (Appendix I) [Note, Module 1 is closed to recruitment]
- Module 2: Durvalumab + AZD9150 (Appendix J) [Note, Module 2 is closed to recruitment per CSP version 10.0]
- Module 3: Durvalumab + AZD6738 (AZD6738 dosed for 7 days as monotherapy, and then for 7 days [from Days 22 to 28] in every 4-week combination cycle) (Appendix K) [Note, Module 3 was re-opened and expanded per CSP version 10.0; per CSP version 12.0, Module 3 is closed to recruitment]
- Module 4: Durvalumab + vistusertib (Appendix L) [Note, Module 4 is closed to recruitment per CSP version 3.1]
- Module 5: Durvalumab + oleclumab (Appendix M) [Note, Cohort B.5.PRI is closed to recruitment per CSP version 7.0; Cohort A.5.73H and Cohort B.5.ACQ are closed to recruitment per CSP version 10.0]
- Module 6: Durvalumab + trastuzumab deruxtecan (DS-8201a) (Appendix N)
- Module 7: Durvalumab + cediranib (AZD2171) (Appendix O) [Note: Module 7 is closed to recruitment.]
- Module 8: AZD6738 monotherapy (AZD6738 dosed for 14 days [from Days 1 to 14] in every 4-week cycle) (Appendix P) [Note, Module 8 is closed to recruitment per CSP version 10.0]
- Module 9: Durvalumab + AZD6738 (AZD6738 dosed for 14 days [from Days 15 to 28] in every 4-week combination cycle) (Appendix Q) [Note, Module 9 is closed to recruitment per CSP version 10.0].
- Module 10: Durvalumab + AZD6738 (AZD6738 at 160 mg and 240 mg dosed for 7 days as monotherapy, and then for 7 days [from Days 22 to 28] in every 4-week combination cycle) (Appendix R).
- Module 11: AZD6738 (ceralasertib) monotherapy (AZD6738 dosed for 7 days at 240 mg [from Days 1 to 7] in every 4-week cycle) (Appendix S).

As shown above, the modules contain study drug-specific information. They include all relevant cohorts, so Modules 1, 3, and 5 contain treatment cohorts for both biomarker-matched and biomarker-non-matched groups. Modules 10 and 11 contain treatment cohorts independent of molecular aberration status. Specific rationales for individual cohorts are provided in the modules.

Figure 4 Study flow diagram



[a] AZD6738 dosed for 7 days as monotherapy, and then for 7 days [from Days 22 to 28] in every 4-week combination cycle.

[b] AZD6738 dosed for 14 days [from Days 1 to 14] in every 4-week cycle.
[c] AZD6738 dosed for 14 days [from Days 15 to 28] in every 4-week combination cycle.
[d] AZD6738 dosed for 7 days as monotherapy [from Days 1 to 7] in every 4-week cycle.

Note, per protocol version 3.1, Module 4 (Durvalumab + vistusertib) is closed to recruitment. Per protocol version 7.0, Cohort B.5.PRI is closed to recruitment. Per protocol v10.0, Module 2 (Cohorts B.2.PRI and B.2.ACQ), Module 5 (Cohorts A.5.73H and B.5.ACQ), Module 8 (Cohort A.8.ATM) and Module 9 (Cohorts B.9.PRI and B.9.ACQ) are closed to recruitment. Per protocol v12.0, Module 1 (Cohorts A.1 and B.1), Module 3 (Cohorts A.3 and B.3) and Module 7 (Cohort B.7) are closed to recruitment. As of protocol v13.0, all modules are closed to recruitment.

ACQ acquired resistance; *ATM* ataxia telangiectasia mutated; CD73 cluster of differentiation 73; HER2 human epidermal growth factor receptor 2; *HRRm* mutation detected in a homologous recombination repair gene; *LKB1* liver kinase B1 (also known as STK11; serine threonine kinase 11); PRI primary resistance; CCI [redacted]

4.1.3 Treatment groups

As of protocol version 13.0, all modules are closed to recruitment.

Group A: Biomarker matched

In this group, patients will have a therapy matched according to their tumour molecular analysis. Each cohort will recruit approximately 20 patients. The rationale for biomarker selection is described in the respective modules.

- Cohorts A.1 will investigate the efficacy, safety, and tolerability of durvalumab given intravenously (IV), in combination with olaparib (AZD2281) given orally (treatment details in Module 1) [Note, Cohort A.1 is closed to recruitment]:
  - Cohort A.1.HRR for patients with detectable aberrations in *HRRm*
  - Cohort A.1.LKB for patients with detectable aberrations in *LKB1* (also known as STK11)
- Cohort A.3.ATM will investigate the efficacy, safety, and tolerability of durvalumab given IV, in combination with AZD6738 given orally, in patients with detectable aberrations in *ATM* (AZD6738 dosed for 7 days as monotherapy, and then for 7 days [from Days 22 to 28] in every 4-week combination cycle) (treatment details in Module 3). [Note, per protocol version 10.0, this cohort was expanded; per protocol version 12.0, this cohort is closed to recruitment].
- Cohort A.4.RIC will investigate the efficacy, safety, and tolerability of durvalumab given IV, in combination with vistusertib (AZD2014) given orally, in patients with detectable amplifications in CCI (treatment details in Module 4). [Note, per protocol version 3.1, Module 4 is closed to recruitment].
- Cohort A.5.73H will investigate the efficacy, safety, and tolerability of durvalumab given IV, in combination with oleclumab (MEDI9447) given IV, in patients expressing high levels of cluster of differentiation (CD)73 protein (treatment details in Module 5). [Note: per protocol version 10.0, this cohort is closed to recruitment]
- Cohorts A.6 will investigate the efficacy, safety, and tolerability of durvalumab given IV, in combination with trastuzumab deruxtecan (DS-8201a) given IV (treatment details in Module 6):
  - Cohort A.6.HER2e for human epidermal growth factor receptor 2 (HER2) expressing patients
  - Cohort A.6.HER2m for patients with selected HER2 mutations. Recruitment to the A.6.HER2m cohort may continue in parallel with recruitment to the A.6.HER2e cohort and will stop once the A.6.HER2e cohort is complete. Due to the low prevalence of HER2 mutations, it is likely that less than 20 patients may be dosed in the A.6.HER2m cohort. The analyses and summaries to be produced will be dependent on the number of patients recruited and will be detailed in the SAP.
- Cohort A.8.ATM will investigate the efficacy, safety, and tolerability of AZD6738 monotherapy given orally for 14 days [from Days 1 to 14] in every 4-week cycle, in

patients with detectable aberrations in *ATM* (treatment details in Module 8). [Note: per protocol version 10.0, this cohort is closed to recruitment].

Group B: Biomarker non-matched

Patients in this group will be prospectively stratified by their prior response to immunotherapy. The biomarker non-matched cohorts will be opened sequentially. Each cohort will recruit approximately 20 patients (approximately 40 patients for cohorts in Module 9, and from implementation of protocol version 10.0, up to approximately 50 patients per non-matched cohort in Module 3) who had either primary resistance or acquired resistance. These terms are defined as:

Primary resistance; patients who had anti-PD-1/PD-L1 containing therapy but had progression of disease (PD) within ≤24 weeks from the start of treatment.

Acquired resistance; patients who had progressive disease >24 weeks from the start of anti-PD-1/PD-L1 containing therapy whilst still on that treatment.

- Cohort B.1 will investigate the efficacy, safety, and tolerability of durvalumab given IV, in combination with olaparib (AZD2281) given orally (treatment details in Module 1), stratified by prior response to immunotherapy; primary resistance (Cohort B.1.PRI) or acquired resistance (Cohort B.1.ACQ). [Note, Cohort B.1 is closed to recruitment].
- Cohort B.2 will investigate the efficacy, safety, and tolerability of durvalumab given IV, in combination with AZD9150 given IV (treatment details in Module 2), stratified by prior response to immunotherapy; primary resistance (Cohort B.2.PRI) or acquired resistance (Cohort B.2.ACQ). [Note, Cohort B.2 is closed to recruitment].
- Cohort B.3 will investigate the efficacy, safety, and tolerability of durvalumab given IV, in combination with AZD6738 given orally (AZD6738 dosed for 7 days as monotherapy, and then for 7 days [from Days 22 to 28] in every 4-week combination cycle) (treatment details in Module 3) stratified by prior response to immunotherapy; primary resistance (Cohort B.3.PRI) or acquired resistance (Cohort B.3.ACQ). [Note, per protocol version 10.0, Cohort B.3 was re-opened and expanded; per protocol version 12.0, Cohort B.3 is closed to recruitment].
- Cohort B.5 will investigate the efficacy, safety, and tolerability of durvalumab given IV, in combination with oleclumab given IV (treatment details in Module 5) stratified by prior response to immunotherapy; primary resistance (Cohort B.5.PRI) or acquired resistance (Cohort B.5.ACQ). [Note, per protocol version 7.0, Cohort B.5.PRI is closed to recruitment and per protocol version 10.0, Cohort B.5.ACQ is closed to recruitment].
- Cohort B.7 will investigate the efficacy, safety, and tolerability of durvalumab given IV, in combination with cediranib given orally (treatment details in Module 7) stratified by prior response to immunotherapy; acquired resistance (Cohort B.7.ACQ). [Note: Cohort B.7.ACQ is closed to recruitment.]
- Cohort B.9 will investigate the efficacy, safety, and tolerability of durvalumab given IV, in combination with AZD6738 given orally for 14 days [from Days 15 to 28] in every

4-week combination cycle (treatment details in Module 9) stratified by prior response to immunotherapy; primary resistance (Cohort B.9.PRI) or acquired resistance (Cohort B.9.ACQ). [Note: per protocol version 10.0, both cohorts are closed to recruitment].

Group C: Molecular aberration independent

Cohorts C.10.160 and C.10.240 in Module 10 will further investigate the efficacy, safety, and tolerability of AZD6738 given orally BD (AZD6738 dosed for 7 days as monotherapy, and then for 7 days [from Days 22 to 28] in every 4-week combination cycle), in combination with durvalumab given IV (treatment details in Module 10), stratified by prior response to immunotherapy; primary resistance or acquired resistance**.**

Cohort C.11.240 in Module 11 will further investigate the efficacy, safety, and tolerability of AZD6738 given orally BD (AZD6738 dosed for 7 days [Days 1 to 7] in every 4-week cycle) in the monotherapy setting, summarised by prior response to immunotherapy; primary resistance or acquired resistance.

Module enrolment

Enrolment to molecular aberration independent cohorts will be prioritised over other modules and will be sequential. Enrolment to biomarker non-matched cohorts will be sequential. The sequential order of enrolment into cohorts will be communicated to sites. In the event that the 'next' sequential module has not yet been approved in all countries, those countries where the next module has been approved may be allowed to enrol patients onto the next module to enable the current module to be completed in countries where the next module has not yet been approved. The AstraZeneca study team will decide when to implement this approach and will inform investigators in advance of implementation of the decision. It is not envisaged this would occur before at least 12 patients have been treated in a module. All such decisions will be documented within the clinical study report. The SoA for each cohort will be included in the appropriate module. Please consult the module for the cohort in which patients are enrolled.

To allow time for all data and samples to be available, such as archival tumour samples and/or a new tumour biopsy, patients may be consented and pre-screened any time before main screening. Moreover, the archival sample can be sent to the central lab for molecular profiling prior to radiological progression on prior PD-1/PD-L1 therapy. Main screening of patients is expected to be undertaken within 28 days prior to the first dose of study drug.

Except for patients in Module 10, patients will not be randomised. A process to control the allocation of patients to cohorts will be implemented. Details of the algorithm used for treatment allocation will be provided in the Pathology and Genomic Testing Manual. This

algorithm will inform treatment allocation in the event that more than one qualifying biomarker is identified.

For details on study drugs given during the study, see the relevant modules.

For details on what is included in the efficacy and safety endpoints, see Section 3.

4.1.4 Clinical screening procedures

At enrolment, each potential patient will provide informed consent prior to starting any study specific procedures. This study has a 2-step consent process, with separate informed consent forms (ICFs).

- Pre-screen consent is required for the pre-screen procedures to take place, where a tumour sample will be analysed, and the patient will be allocated to a treatment cohort. A new tumour biopsy is mandated for all patients. Cohort allocation will be informed by tumour molecular status (except for Group C cohorts), prior response to checkpoint immunotherapy (acquired or primary resistance) and by the cohorts open for recruitment at the time of enrolment. If there is not an open cohort for the which patient is eligible, the patient will be a pre-screen failure (refer to Section 5.4). Patients who consent to pre-screening whilst on prior therapy will be allocated to a cohort at the time of progression on prior therapy. The maximum duration for the pre-screening period is 6 months. Patients in pre-screening for 6 months who are not continuing to main screening will be pre-screen failures. Patients will be given the choice to complete main screening procedures that are common to all modules before their tumour biomarker results are known.
- Main screen consent is then required to enter the treatment period of the study. The 2-step consent is detailed in Section 5.2.1.

Recruitment into the study will be conducted in a controlled manner by AstraZeneca. Unique enrolment codes (E-codes) are assigned automatically when the patient is entered into the study database/interactive response technology (IRT) system after signing pre-screen consent. Results from the pre-screening assessments will inform the appropriate cohort allocation for main screening. For patients who then meet all inclusion/exclusion criteria, AstraZeneca will allocate an additional identifier; a unique, cohort specific, patient number. No patient will be dosed without prior authorisation from the sponsor. Enrolment codes and patient numbers cannot be reused.

The following screening procedures should be undertaken, which are common to each of the modules (please also refer to Table 1):

- Demographic data and other characteristics will be recorded and will include date of birth or age, gender, race and/or ethnicity per local regulations, smoking history.

- A standard medical, medication and surgical history, including prior cancer treatments, response, and duration of response, will be obtained with review of the selection criteria with the patient.
- At pre-screening, patients should be expected to meet the formal eligibility criteria of the core protocol. If they do, they will be allocated to a treatment cohort based on their tumour biomarker results and can proceed to main screening. Patients who are not expected to meet the formal eligibility criteria of the core protocol should not be consented for the study.
- Only patients who are strongly suspected to have disease progression (based on clinical and radiological features as determined by the investigator) or are experiencing disease progression should be enrolled. If the investigator is considering another treatment at this stage, the patient should not be enrolled in the HUDSON study.
- At main screening, consenting patients are assessed to ensure that they meet the module-specific eligibility criteria. Patients who do not meet the module- or cohort-specific criteria of the module they have been allocated to may be re-assigned to the next available and suitable module or cohort as per the allocation algorithm.
- Pre-screen and main-screen fail patients will be followed for survival. (Note, no further survival follow-up is required from implementation of protocol version 10.0; see Section 8.1.3.2).
- All patients will be required to provide consent to supply an archival tumour biopsy sample (if available), a new tumour biopsy, and blood sample for entry into this study. This consent is included in the pre-screen ICF. An archival tumour sample may be used for molecular profiling to accelerate a treatment decision. A new tumour biopsy (post-progression on prior PD-1/PD-L1 therapy) is mandated irrespective of whether an archival tumour sample is available (Module 10 and Module 11 only: specific exemptions for submitting biopsies may apply; see Section 5.1). Where available, plasma CCI [redacted] from blood samples collected at the pre-screening visit may also be used for patient allocation.
- Samples for analysis of a number of biomarkers and assessment of extent of disease.

Following patient consent, data obtained prior to consent may be used for screening provided the assessments fall within the protocol specified period prior to the first dose of study drug. Screening procedures that are specific to each module are described in the appropriate modules. The pre-screen assessment of tumour samples for the presence of molecular alterations required for treatment cohort allocation may be performed outside the 28-day screening window (ie, pre-screen, as shown in Figure 1). Moreover, the archival sample can be sent to the central lab for molecular profiling prior to radiological progression on prior PD-1/PD-L1 therapy. The timing of blood sample collection in pre-screening for central laboratory molecular profiling, in relation to patient status on immediate prior therapy, will be clarified in the Pathology and Genomics Testing Manual.

Samples for the assessment of safety laboratory tests will be sent to a local laboratory and assessed locally. All other samples such as those for the assessment of molecular aberrations

and exploratory biomarkers will be assessed centrally. The tumour sample(s) taken as part of the pre-screen procedures will be sent to a central laboratory(ies) for analysis of molecular alterations using tests verified and validated in line with local regulations eg, Clinical Laboratory Improvement Amendments/College of American Pathologists (CLIA/CAP) for US laboratories, Good Clinical Practice (GCP), and local accreditation for other territories.

4.1.5 Regulatory amendment for additional modules

To support amendment of the protocol for additional modules/cohorts, including any non-comparative randomised expansion cohorts, AstraZeneca will provide a summary of the available data to support the proposed treatment module/cohort, as follows:

Europe and Rest of World

AstraZeneca will provide a substantial amendment for review and approval.

United States of America

AstraZeneca will provide an amendment to the FDA approximately 30 days in advance of planned enrolment into any new cohort. AstraZeneca will begin enrolment of patients into that cohort in the United States after Institutional review board (IRB) approval.

4.1.6 Study conduct mitigation during study disruptions due to cases of civil crisis, natural disaster, or public health crisis

The guidance given below supersedes instructions provided elsewhere in this protocol and should be implemented only during cases of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions, and considerations if site personnel or study patients become infected with SARS-CoV-2 or similar pandemic infection) which would prevent the conduct of study-related activities at study sites, thereby compromising the study site staff or the patient's ability to conduct the study. The investigator or designee should contact the study sponsor to discuss whether the mitigation plans below should be implemented.

To ensure continuity of the clinical study during a civil crisis, natural disaster, or public health crisis, changes may be implemented to ensure the safety of study patients, maintain compliance with GCP, and minimise risks to study integrity.

Where allowable by local health authorities, ethics committees, healthcare provider guidelines (eg, hospital policies) or local government, these changes may include the following options:

- Obtaining consent/reconsent for the mitigation procedures (note, in the case of verbal consent/reconsent, the ICF should be signed at the patient's next contact with the study site).

- Telemedicine visit: Remote contact with the patients using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.
- Delivery of oral investigational product administration from site to the patient's home if allowed as per the institution guidance and applicable regulations.

4.2 Scientific rationale for study design

4.2.1 Unmet need in NSCLC

As described in Section 2.2, current therapies for metastatic NSCLC patients who have received immune checkpoint and platinum-doublet therapies have poor outcomes, so there is still a significant unmet medical need for additional treatment options for this patient population.

4.2.2 Rationale for conducting this study

This is an open-label, multi-centre, umbrella Phase II study in patients who have received an anti-PD-1/PD-L1 containing therapy and a platinum-doublet regimen for locally advanced or metastatic NSCLC either separately or in combination. The patient must have had disease progression on a prior line of anti-PD-1/PDL1 therapy. This study is modular in design, allowing initial assessment of the efficacy, safety, tolerability of multiple treatment arms.

There is currently no established therapy for these patients, and novel treatments are urgently needed.

4.2.3 Rationale for study design

The study will consist of a number of treatment cohorts, evaluating the efficacy, safety and tolerability of specific study drugs.

An open-label design is needed for this study due to the different schedules and methods of administration of treatments in the study (IV and oral).

The sponsor plans to include investigations into inter- and intra-individual variability in exploratory biomarker and pharmacodynamic profiles and their relationship to drug effect. These biomarkers may be derived from tissue and/or blood and include the analyses of cells, DNA, RNA, proteins and/or metabolites. There are many potential benefits of this exploratory research, including the possibility to identify patients most likely to benefit from these treatments or novel targeted agents and combinations, explain outliers or non-responders or explain AEs related to drug exposure. This research may result in an understanding of the impact of variation between individuals and how this information can be utilised to bring better drugs to the clinic.

For Groups A and B, assignment of patients to treatment arms will be made based upon the status of the relevant molecular aberration in a patient's tumour. The strength of clinical

hypothesis as well as the prevalence of each aberration will be considered when overlapping or co-occurring aberrations are encountered. For example, well-established clinically actionable mutations such as breast cancer associated gene 1/2 (*BRCA1/2*), as well as low-prevalence aberrations will be prioritised to ensure adequate recruitment for each cohort. Guidelines to inform cohort allocation for patients with overlapping aberrations or more than a single qualifying aberration will be included in the Pathology and Genomic Testing Manual.

CCI in the context of CCI 2 additional modules have been included in the HUDSON study (Group C): Module 10 (optimal CCI added in protocol amendment 10.0) and Module 11 (CCI added in protocol amendment 11.0).

4.3 Justification for dose

Information on dose justification is provided in the respective modules.

4.4 End of study definition

For the purpose of Clinical Trial Transparency (CTT) the definition of the end of the study differs under FDA and EU regulatory requirements:

European Union requirements define study completion as the last visit of the last subject for any protocol related activity.

Food and Drug Administration requirements defines 2 completion dates:

Primary Completion Date – the date that the final participant is examined or receives an intervention for the purposes of final collection of data for the primary outcome measure, whether the clinical study concluded according to the pre-specified protocol or was terminated. In the case of clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes.

Study Completion Date – the date the final participant is examined or receives an intervention for purposes of final collection of data for the primary and secondary outcome measures and AEs (for example, last participant's last visit), whether the clinical study concludes according to the pre-specified protocol or is terminated.

Last Subject Last Visit for the study is defined as the date of the 12-month visit post last patient in the last active cohort that started the study treatment (final data cut-off). The database will be closed and no further data will be captured. Study sample collection will also be considered completed at this time and all remaining samples at site should be shipped as soon as possible to the respective laboratory as per laboratory manual.

The study may be terminated at individual centres if the study procedures are not being performed according to GCP, or if recruitment is slow.

AstraZeneca may also terminate the entire study or individual cohorts prematurely if concerns for safety arise or a negative benefit/risk is concluded, within this study or in any other study with any agent used in any of the study modules. This will result in shortening the 12-month visit period post last patient in this terminated cohort.

Patients who are receiving treatment following database lock for the final analysis can either choose to discontinue from the study or, where the investigator believes patients are gaining clinical benefit, patients may continue to receive study treatment following discussion with, and approval from, the sponsor in accordance with Section 8.3.14. All patients will receive follow-up care in accordance with standard local clinical practice. For patients who do continue to receive treatment beyond the time of the final database lock, investigators will continue to report all non-serious adverse events (AEs) and serious adverse events (SAEs), pregnancy, and overdose until 90 days after the last dose of study treatment, in accordance with Section 8.4.1 using paper forms. Additionally, any SAE that is ongoing at the time of the final database lock must be followed up to resolution unless the event is considered by the investigator to be unlikely to resolve, or the patient is lost to follow-up.

See Appendix A 6 for guidelines for the dissemination of study results.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study in order to be assigned to a study cohort. Under no circumstances can there be exceptions to this rule. Patients who do not meet the entry requirements are screen failures, refer to Section 5.4.

Patients must meet the inclusion and exclusion criteria of both the core and module protocol. Where there are differences in stringency or cut-off values, the specific module takes precedence. For example, if haematological medication parameters are stricter in the module rather than core, the investigator should adhere to the module criteria.

In this protocol, ‘enrolled’ patients are defined as those who sign informed pre-screen consent. Each enrolled patient is identified by their unique E-code. ‘Allocated’ patients are defined as those who are assigned to a treatment cohort. Patients who meet all inclusion and exclusion criteria will be assigned an additional unique patient number prior to first dose.

For procedures for withdrawal of incorrectly enrolled patients see Section 7.3.

5.1 Inclusion criteria

The inclusion criteria that are applicable to all cohorts in the study are described in this section. Please also refer to the relevant module for specific criteria applicable to each cohort. Where criteria are more stringent in the module rather than the core, the investigator should adhere to the module criteria.

Subjects are eligible to be included in the study only if all of the following inclusion criteria and none of the exclusion criteria apply:

Informed consent

1 Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the ICF and in this protocol. A legally authorised representative may sign on behalf of the patient.

2 Provision of signed and dated, written informed consent form prior to any mandatory study specific procedures, sampling, and analyses.

Pharmacogenetic research study (optional)

For inclusion in the optional (DNA) genetics research, study patients must fulfil the following criteria:

- Provide informed consent for the genetic sampling and analyses.

If a patient declines to participate in the genetics research, there will be no penalty or loss of benefit to the patient. A patient who declines genetics research participation will not be excluded from any other aspect of the main study.

The ICF process is described in Appendix A 3. Full details on optional genetic research are included in Appendix D.

Age

3 At least 18 years of age at the time of signing the informed consent form.

Type of patient and disease characteristics

4 Patient must have histologically or cytologically confirmed metastatic or locally advanced and recurrent NSCLC which is progressing.

5 Patients eligible for second- or later-line therapy, who must have received an anti-PD-1/PD-L1 containing therapy and a platinum-doublet regimen for locally advanced or metastatic NSCLC either separately or in combination. Prior durvalumab is acceptable. The patient must have had disease progression on a prior line of

anti-PD-1/PD-L1 therapy. Importantly, please refer to exclusion #16 for the requirements for prior anti-PD-1/PD-L1 therapy.

6 Suitable for a new tumour biopsy (unless the patient has had a biopsy post-progression on an anti-PD-1/PD-L1 containing therapy, and within approximately 3 months of main screen consent). For Module 10 and Module 11 only: If in agreement with the sponsor study physician, a patient may be exempt from a biopsy at pre-screening if a tumour tissue sample is obtained after progression on prior anti-PD-(L)1 therapy and ≤ 3 months prior to pre-screening; if no such sample is available, a tumour sample taken after progression on prior anti-PD-(L)1 therapy and within the previous 24 months is acceptable. Note: For patients in Modules 1 to 5 only to be re-allocated to a second treatment on this study: provision of a tumour biopsy following disease progression on the first therapy, prior to re-allocation to the second treatment.

7 Eastern Cooperative Oncology Group/World Health Organization (ECOG/WHO) performance status of 0 to 1 with no deterioration between screening and the first dose of study treatment, and a minimum life expectancy of 12 weeks (see Section 8.2.5).

8 Patient must have at least 1 lesion that can be accurately measured at pre-dose as ≥10 mm in the longest diameter (except lymph nodes which must have short axis ≥15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) and which is suitable for accurate repeated measurements (not applicable for patients to be re-allocated to a second treatment on this study). This lesion should not be used for biopsy unless there are no other lesions suitable for biopsy (see Section 8.8.1.2). A previously irradiated lesion can be considered a target lesion if the lesion has clearly progressed.

9 Patient must have had a treatment-free interval of ≥3 weeks from any prior therapy before the start of study drug. [For re-allocated patients in Modules 1 to 5 only, a treatment-free interval of anything less than 3 weeks, must be agreed with the study physician]. The following intervals between the end of the prior treatment and first dose of study drug must be observed:

   (a) Minor surgical procedures (as defined by the investigator): 7 post-operative days.

   (b) Major surgery (as defined by the investigator): ≥4 weeks.

   (c) Radiotherapy: ≥4 weeks (patients who receive palliative radiation for nontarget tumour lesions need not be subjected to this washout period and can be enrolled immediately).

Weight

10 Body weight >30 kg and no cancer-associated cachexia (eg, common terminology criteria for adverse events [CTCAE] Grade 2 or worse weight loss over the past 3 months).

Reproduction

11 Evidence of post-menopausal status or negative urinary or serum pregnancy test for female pre-menopausal patients. Women will be considered post-menopausal if they

have been amenorrhoeic for 12 months without an alternative medical cause. The following age-specific requirements apply (age requirements not applicable for Module 6; see Section 5.1 of module):

Women <50 years of age would be considered post-menopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinising hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilisation (bilateral oophorectomy or hysterectomy).

Women ≥50 years of age would be considered post-menopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilisation (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

See also reproduction inclusion criteria applicable to individual modules in the respective module.

5.2 Exclusion criteria

The exclusion criteria that are applicable to all cohorts in the study are described in this section. Please also refer to each specific module for specific criteria applicable to each cohort. Where criteria are more stringent in the module rather than the core, the investigator should adhere to the module criteria. Patients must not enter the study if any of the following exclusion criteria apply:

Medical conditions

1 Patients whose tumour samples have targetable alterations in *EGFR* and/or *ALK* at initial diagnosis are excluded. In addition, patients whose tumour samples are known to have targetable alterations in *ROS1, BRAF, MET* or *RET*, are to be excluded. Note: where *ROS1, BRAF, MET* and/or *RET* biomarker status is unknown from pre-existing local data, and the patient's tumour sample harbours one of the study inclusion biomarkers, please refer to Section 5.2.1.3 and Section 7.3. Information on targetable alterations is provided in the Pathology and Genomics Testing manual and may be updated with emerging information. For Modules 10 and 11 only, see specific exclusion criteria in the respective module.

2 History of allogenic organ transplantation

3 Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [eg, colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or

Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc]). The following are exceptions to this criterion:

- Patients with vitiligo or alopecia
- Patients with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement
- Any chronic skin condition that does not require systemic therapy
- Patients without active disease in the last 5 years may be included but only after consultation with the study physician
- Patients with celiac disease controlled by diet alone

4 Uncontrolled intercurrent illness, including but not limited to: ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhoea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase the risk of incurring AEs or compromise the ability of the patient to give written informed consent.

5 History of another primary malignancy except for:

- Malignancy treated with curative intent and with no known active disease ≥2 years before the first dose of study drug and of low potential risk for recurrence
- Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
- Adequately treated carcinoma in situ without evidence of disease
- Localised non-invasive primary under surveillance

6 Active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and tuberculosis testing in line with local practice), hepatitis B (known positive HBV surface antigen [HBsAg] result), hepatitis C, or human immunodeficiency virus (positive HIV 1/2 antibodies). Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for hepatitis C (HCV) antibody are eligible only if the polymerase chain reaction is negative for HCV RNA.

Participants co-infected with HBV and HCV, or co-infected with HBV and hepatitis D virus (HDV), namely: HBV positive (presence of HBsAg and/or anti HBcAb with detectable HBV DNA); AND

- HCV positive (presence of anti-HCV antibodies); OR
- HDV positive (presence of anti-HDV antibodies).

7 Female patients who are pregnant or breastfeeding, or male or female patients of reproductive potential who are not willing to employ highly effective birth control from screening to 7 months (females) or 6 months (males) after the last dose of study drug.

8 Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients, or history of severe hypersensitivity reactions to other monoclonal antibodies.

9 Patients must not have experienced a toxicity that led to permanent discontinuation of prior anti-PD-1 or anti PD-L1 immunotherapy.

- All AEs while receiving prior immunotherapy must have completely resolved or resolved to baseline prior to screening for this study.
- Patients must not have experienced a ≥Grade 3 immune-related AE or an immune-related neurologic or ocular AE of any grade while receiving prior immunotherapy. Note: Patients with endocrine AE of ≤Grade 2 are permitted to enrol if they are stably maintained on appropriate replacement therapy and are asymptomatic.

Note: Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment may be included only after consultation with the study physician. Patients with CTCAE Grade ≤2 peripheral neuropathy from prior chemotherapy will be eligible.

- Patients must not have required the use of additional immunosuppression other than corticosteroids for the management of an AE, not have experienced recurrence of an AE if re-challenged, and must not currently require maintenance doses of >10 mg prednisone or equivalent per day.

10 Patient has spinal cord compression or symptomatic brain metastases. Note: Patients with asymptomatic, radiographically stable brain metastases and not requiring steroids for symptomatic management will be eligible, as well as patients who have completed definitive therapy, are not on steroids, and have a stable neurologic status for at least 2 weeks after completion of the definitive therapy and steroids.

11 (Deleted with Clinical Study Protocol [CSP] version 3)

12 Patient has small cell lung cancer (SCLC).

Prior/concomitant therapy

13 Any concurrent chemotherapy, immunotherapy, biologic or hormonal therapy for cancer treatment. Concurrent use of hormones for non-cancer-related conditions (eg, insulin for diabetes and hormone replacement therapy) is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable (eg, by local surgery or radiotherapy).

- Patients may receive treatment with bisphosphonates or receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors for the treatment of bone metastases.

14 Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab. The following are exceptions to this criterion:

- Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra-articular injection)

- Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent
- Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication)

15 Receipt of live attenuated vaccine within 30 days prior to the first dose of study drug.
Note: Patients, if enrolled, should not receive live vaccine whilst receiving study drug and up to 180 days after the last dose of study drug. Authorised and approved COVID-19 vaccines are allowed; however, it is recommended to avoid their administration for 72 hours prior to administration of the first dose of study treatment.

16 Patients who have received more than one line of previous therapy with an anti-PD-1/PD-L1 agent, either alone or in any combination, are excluded, as follows:

- Patients who have received two or more prior lines of an anti-PD-1/PD-L1 therapies with DIFFERENT anti-PD-1/PD-L1 therapies, are excluded. This does not apply to patients considered for the optional re-allocation to a different treatment cohort in HUDSON.
- Patients who discontinued treatment with an anti-PD-1/PD-L1 therapy for a reason other than disease progression or significant toxicity (refer to exclusion 5.2.9) and have been retreated with the SAME anti-PD-1/PD-L1 therapy again, may be included if they had disease progression on the treatment (refer to inclusion 5.1.5).

Diagnostic assessments

17 Patient has any of the following cardiac criteria:

(a) Mean QT interval corrected for heart rate (QTc) ≥470 ms calculated from 3 electrocardiograms (ECGs) using Fridericia's correction.

(b) Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG eg, complete left bundle branch block, third degree heart block, second degree heart block, first degree heart block.

(c) Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalaemia, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years of age or any concomitant medication known to prolong the QT interval.

(d) Uncontrolled hypertension – blood pressure (BP) ≥150/95 mmHg despite medical therapy.

(e) Unstable atrial fibrillation or unstable cardiac arrhythmia with a ventricular rate >100 bpm on an ECG at rest.

(f) Symptomatic heart failure – New York Heart Association Grade II to Grade IV.

(g) Prior or current cardiomyopathy.

(h) Severe valvular heart disease.

(i) Uncontrolled angina (Canadian Cardiovascular Society Grade II to Grade IV despite medical therapy) or acute coronary syndrome within 6 months prior to screening.

(j) Patients at risk of brain perfusion problems eg, carotid stenosis. Stroke or transient ischaemic attack in the last 6 months prior to screening.

18 Patient has inadequate bone marrow reserve or organ function as demonstrated by any of the following laboratory values:

(a) Absolute neutrophil count $<1.0 \times 10^9$/L.

(b) Platelet count $<75 \times 10^9$/L.

(c) Haemoglobin <9.0 g/dL.

(d) Alanine aminotransferase (ALT) >2.5 × the upper limit of normal (ULN) if no demonstrable liver metastases or >5 × ULN in the presence of liver metastases.

(e) Total bilirubin (TBL) >1.5 × ULN or for patients with documented/suspected Gilbert's disease, bilirubin ≥2 × ULN.

(f) Creatinine clearance <40 mL/min calculated by Cockcroft-Gault equation (see Table 5 for calculation).

Other exclusions

19 Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).

20 Any medical, psychological, or social condition which would make it difficult for the participant to participate in the study and to comply with the study procedures, restrictions and requirements

For patients who consent to the optional genetic sample

21 Previous allogenic bone marrow transplant.

22 Non-leukocyte depleted whole blood transfusions within 120 days of the date of the genetic sample collection.

For procedures for withdrawal of incorrectly enrolled patients see Section 7.3.

New criteria per protocol version 6:

23 History of active primary immunodeficiency.

5.2.1 Two-step consent process

As detailed in Section 4.1, patients will be stratified into the appropriate treatment cohort based on the confirmation of biomarkers (molecular aberrations) detected in biological samples (except for Group C cohorts), and the patient's prior response to an anti-PD-1/PD-L1-containing therapy. Pre-screening informed consent of study procedures and collection of tumour samples may be obtained prior to the 28-day main screening window, if necessary, to

permit tumour biopsy sample acquisition and analysis prior to main screen assessments. Moreover, the archival sample can be sent to the central lab for molecular profiling prior to radiological progression on prior PD-1/PD-L1 therapy.

5.2.1.1 Pre-screen consent

Pre-screen consent includes access to pre-existing molecular information (if available), testing of an archival tumour sample (if available) and/or plasma CCI and provision of a new tumour biopsy sample and blood sample for CCI testing.

The pre-existing molecular information used for patient assignment must have been obtained using a validated test in accordance with local regulations (eg, CLIA/CAP accreditation in the US). Patients with an existing ataxia telangiectasia mutated (ATM), CD73 or HER2 immunohistochemistry (IHC) result will not be enrolled into the study on the basis of this result, IHC data generated at the central laboratory(s) will be used for allocation to cohort A.3.ATM, cohort A.5.73H and cohort A.6.HER2e.

The new tumour biopsy must be collected post-progression on prior PD-1/PD-L1 therapy. Where a patient has had a biopsy within approximately 3 months of the date of main screen consent, and the tumour content is adequate to meet study objectives, the recent biopsy sample may be submitted. The new tumour biopsy will be used for prospective molecular testing, or confirmation of the results obtained from the archival sample or prior local molecular test. Every effort should be made to collect the new biopsy during pre-screening. The new biopsy may be taken during main screening if for any reason it cannot be obtained during pre-screening. Refer to Section 5.1, inclusion criterion 6 for details of the potential exemption for Modules 10 and 11 patients to provide a new tumour biopsy at pre-screening.

To shorten patients' waiting time before allocation and treatment, patients will be given the choice to undergo main screening assessments prior to their biomarker results being known. The assessments will be those that are common to all modules. Explanations about potential ineligibility when the biomarker results are known will be included in the ICF.

5.2.1.2 Main screen consent

Following pre-screening, and a valid molecular analysis result, the patient will be assigned a treatment cohort. The process for allocation will be detailed in the Pathology and Genomic Testing Manual, and allocation will be documented in the electronic case report form (eCRF).

Once the allocation is made the patient will be invited to consent to a specific treatment cohort. There will be a main ICF for each of the treatment regimens.

Main-screen consent leads to enrolment onto the assigned cohort, and includes consent to mandatory on-treatment biopsies after 6 ± 2 weeks. Biopsies on progression are mandatory only for patients in Modules 1 to 5 who are re-allocated to a different treatment cohort.

Molecular profiling of biopsies at point of disease progression may inform post-progression choice of therapy, including access to another study drug treatment.

There will be a second round of main-screen consent for patients in Modules 1 to 5 who wish to be re-allocated to a different treatment cohort following analysis of the disease progression tumour biopsy. The second treatment regimen would require fewer on-treatment assessments and sampling, as described in Section 7.4 and the SoA in the relevant modules.

Note, from implementation of protocol version 10.0, treatment re-allocation of patients is no longer applicable.

A schematic of the pre-screening process is shown in Figure 5.

Figure 5 Schematic of the two-step consent process

Note: It may be possible to allocate patients to the biomarker non-matched cohort if the local test contains the pre-defined list of HUDSON biomarkers (refer to Pathology and Genomic Testing Manual).
Note: Patient allocation to Group C (Module 10: Cohort C.10.160 and Cohort C.10.240; Module 11: Cohort C.11.240) will be independent of their molecular aberration status.

5.2.1.3 Consent based on biomarker status

All patients must provide pre-screening consent for determination of biomarker status and for a new tumour biopsy to be taken. Consent for pre-screening may be undertaken at any time.

It is envisaged that a number of patients will have pre-existing local molecular profile data from analysis of a previously-archived tissue or blood sample (ATM deficiency, CD73 high or

HER2 expression identified using local IHC tests are not accepted). If so, pre-screen consent will be sought for these data to be analysed for aberrations which can be aligned to a biomarker-matched treatment cohort (or assigned to Group C cohorts). Pre-screen consent must also be obtained for a new tumour biopsy sample to be provided, which will be submitted for retrospective confirmation of biomarker status.

However, if the analysis of the pre-existing local molecular profile data does not identify a pre-defined molecular aberration to allow the patient to be aligned to a biomarker-matched cohort, a tumour sample will be submitted for prospective central testing. Either the analysis will identify aberrations that will align to a biomarker-matched cohort, or no pre-defined biomarkers will be identified, and the patient will be assigned to a biomarker non-matched cohort. In the event that a patient has an identified biomarker for a biomarker-matched cohort and is unable to be enrolled, for example because it is full or completed, the patient will be allocated to the next appropriate cohort open at the time. Group C patients are assigned irrespective of biomarker status. For module specific details, refer to the individual modules.

The FoundationOne CDx Assay (F1CDx) was approved by the FDA on Nov 30, 2017 (PMA P170019) for the detection of specific genomic alterations for therapeutic decision-making and for molecular profiling (https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019C.pdf). Tissue samples from patients with local results generated using this assay may not need to be re-tested at the central laboratory (see Pathology and Genomics Testing Manual for further info). Tissue samples from patients with local results generated according to the protocols of CCI likewise may not need to be re-tested at the central laboratory. These data must not be used for therapeutic decision-making beyond any existing companion diagnostic approvals.

These assessments, to determine the presence of the pre-defined molecular aberrations, must be completed prior to main-screen consent. For patients enrolled into Modules 10 and 11 (Group C), patients can proceed to main screening and dosing without waiting on central test results for pre-defined molecular aberrations.

All screening procedures agreed to as part of the main-screen consent should be performed within 28 days prior to the start of treatment as per study plan. The patient may reconsent if main-screen procedures are not completed within the 28-day window. Reconsent may require that assessments are repeated in order to comply with the 28-day window for main-screen procedures.

Patients may complete the pre-screening consent process via one of the following scenarios:

For patients with known pre-existing aberrations only

- Patients must sign pre-screen consent to provide pre-existing local test result, from either an archived tumour sample or a plasma CCI sample with subsequent retrospective

confirmatory test; patients should have a positive result for one of the predefined molecular aberrations (Group A) for the modules in HUDSON.

- In this instance, patients must provide:
  - Consent to access the pre-existing local test result molecular aberrations and to provide a copy of the redacted laboratory molecular report
  - Consent to the provision of an archival tumour biopsy sample (if available) and a new tumour sample (mandatory; see Section 5.1 CCI [redacted] to perform retrospective confirmation of biomarker status and other translational research
  - Consent to the provision of a blood sample.

For patients with no known pre-existing aberrations

For patients where no pre-existing test data are available, or where pre-existing test data are available but a biomarker of interest was not detected, or where the investigator wishes to submit a new tumour sample for analysis, patients must provide:

- Consent to the provision of a new tumour sample
- Consent to the provision of an archival tumour sample (if available)
- Consent to the provision of a blood sample
- Consent to central testing; a patient's tumour mutation status will be determined by undertaking central testing to establish the presence of a molecular aberration for the biomarker-matched modules in HUDSON. Where central testing is performed on an archival tumour sample a new tumour sample remains mandatory. The new tumour sample will be used for confirmation of treatment allocation (from the molecular analysis of the archival sample).
- Where *ROS1, BRAF, MET* and/or *RET* status is unknown from pre-existing data but is detected for the first time during the prospective testing, the treating physician will be informed (see Section 7.3). This central test result must not be used for therapeutic decision-making beyond any existing companion diagnostic approvals. Cohort allocation will not be delayed to determine *ROS1, BRAF, MET or RET* status, for patients harbouring a HUDSON inclusion marker based on pre-existing molecular test data or for patients allocated to Group C cohorts (molecular aberration independent).
- Further details on sample processing, handling and shipment are provided in the Laboratory Manual. Information on targetable alterations in *EGFR*, *ALK, ROS1, BRAF, MET and RET* is provided in the Pathology and Genomic Testing Manual.

5.3 Lifestyle restrictions

Please refer to the relevant modules. Where restrictions are more stringent in the module rather than the core, the investigator should adhere to the module criteria.

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The following restrictions apply while the patient is receiving study treatment and for the specified times before and after:

Female patients of childbearing potential who are sexually active with a non-sterilised male partner must use at least two highly effective methods of contraception (see Table 4) from the time of screening and must agree to continue using such precautions for 7 months after the last dose of study drug. Male partners of a female patient must use male condom plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Female patients should refrain from breastfeeding throughout this period. In addition, female patients must refrain from egg donation while on study and for 7 months after the final dose of any study drug.

Non-sterilised male patients who are sexually active with a female partner of childbearing potential must use male condom plus spermicide from screening through 6 months after the last dose of study drug. Male patients should refrain from sperm donation throughout this period. Female partners of a male patient must use a highly effective method of contraception throughout this period.

Females of childbearing potential are defined as those who are not surgically sterile (ie, bilateral tubal ligation, salpingectomy, bilateral oophorectomy, or complete hysterectomy) or post-menopausal (defined as 12 months with no menses without an alternative medical cause).

Acceptable non-hormonal birth control methods include:

- Total/True abstinence: When the patient refrains from any form of sexual intercourse and this is in line with their usual and/or preferred lifestyle; this must continue for the total duration of the study and for at least 7 months after the last dose of study drug. Note: Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods, or declaration of abstinence solely for the duration of a study) and withdrawal are not acceptable methods of contraception.
- Total sexual abstinence. Abstinence must continue for the total duration of study treatment and for at least 7 months after the last dose of study drug. Periodic abstinence (eg, calendar ovulation, symptothermal post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Vasectomised sexual partner PLUS male condom. With participant assurance that partner received post-vasectomy confirmation of azoospermia.
- Tubal occlusion PLUS male condom
- Intrauterine device (IUD) PLUS male condom. Coils must be copper-banded.

Highly effective methods of contraception are described in Table 4. A highly effective method of contraception is defined as one that results in a low failure rate (ie, less than 1% per

year) when used consistently and correctly. Note that some contraception methods are not considered highly effective (eg, male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non-copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding Cerazette/desogestrel which is considered highly effective]; and triphasic combined oral contraceptive pills).

Table 4 Highly effective methods of contraception

Barrier/Intrauterine Methods	Hormonal Methods
Copper T intrauterine device	Implants: Etonogestrel-releasing implants: eg, Implanon® or Norplan®
Levonorgesterel-releasing intrauterine system (eg, Mirena®)[a]	Intravaginal Devices: Ethinylestradiol/etonogestrel-releasing intravaginal devices: eg, NuvaRing®
	Injection: Medroxyprogesterone injection: eg, Depo-Provera®
	Combined Pill: Normal and low dose combined oral contraceptive pill
	Patch: Norelgestromin/ethinylestradiol-releasing transdermal system: eg, Ortho Evra®
	Minipill: Progesterone based oral contraceptive pill using desogestrel: Cerazette® is currently the only highly effective progesterone-based pill

[a] This is also considered a hormonal method

5.4 Screen failures

Screen failures are defined as patients who signed the pre-screen ICF to participate in the clinical study but are not subsequently assigned to study treatment or do not meet the criteria for participation in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Patients who do not meet the criteria for participation in this study (screen failures) may be rescreened. Rescreened patients should keep the same patient E-code as for the initial screening and all screening assessments should be within a 28-day window. However, re-screening should be documented so that its effect on study results, if any, can be assessed. Patients who fail screening should have the reason recorded in the eCRF to indicate them as screen failures.

Information will be collected from all patients screened (see SoA, Table 1). For screen failures, this will include demography, screen failure details, eligibility criteria, and any SAEs. Patients who screen fail, and patients who do not receive study treatment for any reason, will be followed for survival, from the date they were identified as having screen failed, and have data collected for subsequent anti-cancer treatments and vital status (dead or alive; date of death) (Section 8.1.3.2). In addition, a blood sample for plasma CCI testing will be collected from all patients in pre-screening in order to evaluate CCI Note: from implementation of protocol version 10.0, patients who screen fail will no longer be followed up for survival; screen fail patients enrolled under earlier versions of the protocol will have their last survival assessment recorded and end study participation.

6. STUDY TREATMENTS

Please refer to the relevant module. Toxicity management guidelines for durvalumab are provided in the Site Master File. Toxicity management guidelines for trastuzumab deruxtecan are provided in Module 6.

7. DISCONTINUATION OF TREATMENT AND PATIENT WITHDRAWAL

7.1 Discontinuation of study treatment

Subjects may be discontinued from study treatment in the following situations. Note that discontinuation from study treatment is NOT the same as a complete withdrawal from the study:

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment.
- Any AE that meets criteria for discontinuation as defined in the Dosing Modification and Toxicity Management Guidelines.
- Initiation of alternative anticancer therapy including another investigational agent
- Severe non-compliance with the CSP.
- Disease progression per RECIST 1.1 unless, in the opinion of the investigator, the patient is still receiving clinical benefit. These patients may continue treatment if none of the other discontinuation criteria are met. In addition, patients will continue receiving scheduled radiological scans as per Section 8.1.1 for as long as the patient is undergoing study treatment.
- Symptomatic deterioration. Note: Patients with rapid tumour progression or with symptomatic progression that requires urgent medical intervention will not be eligible to continue to receive treatment.

- Patients incorrectly initiated on study treatment (eg, patient is determined to have met one or more of the exclusion criteria for study participation at study entry and continuing investigational therapy might constitute a safety risk).
- Pregnancy or intent to become pregnant.

See the SoA in the relevant module for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed. In the drug combination cohorts, one study drug can be withdrawn but the other treatment continued if required.

7.1.1 Treatment interruption

Please refer to the relevant module. Please also refer to the durvalumab toxicity management guidelines for temporary interruptions in durvalumab treatment.

Treatment interruption for toxicity management is allowed for both or either drug in any individual combination treatment arm. If treatment-related adverse events can clearly be assigned to one of the study drugs, and where, in the opinion of the investigator, the patient may still receive clinical benefit, patients may continue with the other drug as monotherapy until disease progression.

7.1.2 Procedures for discontinuation of study treatment

If study treatment is stopped, the investigator should instruct the patient to contact the site before or at the time it is stopped. A patient who decides to discontinue study treatment will always be asked about the reason(s) and the presence of any AEs. The date of last intake of study treatment should be documented in the eCRF. All study treatment should be returned by the patient at their study drug discontinuation visit, which should take place 28 days from the end of treatment date (+/- 7 days). Patients permanently discontinuing study treatment should be given locally available standard of care therapy, at the discretion of the investigator.

Discontinuation of study treatment, for any reason, does not impact on the patient´s participation in the study. The patient should continue attending subsequent study visits and data collection should continue according to the study protocol. If the patient does not agree to continue in-person study visits, a modified follow-up must be arranged to ensure the collection of endpoints and safety information. This could be a telephone contact with the patient as per original scheduled visit intervals, a contact with a relative or treating physician, or information from medical records. The approach taken should be recorded in the medical records. A patient who agrees to modified follow-up is not considered to have withdrawn consent or to have withdrawn from the study.

7.2 Lost to follow-up

A patient will be considered potentially lost to follow-up if he/she fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule.
- Before a patient is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the patient or next of kin (where possible, 2 attempts will be made using either telephone calls, certified letter to the patient´s last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Efforts to reach the patient should continue until the end of the study. Should the patient be unreachable at the end of the study the patient should be considered to be lost to follow-up with unknown vital status at end of study and censored at latest follow-up contact.

7.3 Withdrawal from the study

A patient may withdraw from the study (eg, withdraw consent), at any time (study drug **and** assessments) at his/her own request, without prejudice to further treatment, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or compliance reasons. The reason for patient withdrawal will be recorded in the eCRF.

A patient who considers withdrawing from the study must be informed by the investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).

If the patient withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a patient withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried out in line with what was stated in the informed consent and local regulation. The investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.

A patient who withdraws consent will always be asked about the reason(s) and the presence of any AEs. The investigator will follow up patients as medically indicated.

AstraZeneca or its delegate will request investigators to collect information on patients' vital status (dead or alive; date of death when applicable) at the end of the study from publicly available sources, in accordance with local regulations. Knowledge of the vital status at end of study in all patients is crucial for the integrity of the study.

See the SoA in the relevant module for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. All study treatment should be returned by the patient.

If a patient withdraws from participation in the study, then his/her enrolment code cannot be reused. Withdrawn patients will not be replaced.

Patients assigned to a biomarker-matched cohort, and whose biomarker status is not confirmed by central test(s) of the new tumour biopsy, may be replaced at the discretion of AstraZeneca. Patients assigned to a cohort, for whom one or more of the exclusion biomarkers are detected for the first time during retrospective confirmation of biomarker status, may be replaced at the discretion of AstraZeneca. This should ensure sufficient patients with the appropriate biomarker are assigned to each biomarker-matched cohort prior to an analysis of approximately 20 evaluable patients in each separate cohort.

Investigators will be informed of the central molecular test data and investigators should assess the benefit of ongoing treatment in the event that the biomarker is not confirmed by the central test(s), or a targetable alteration in *EGFR, ALK, ROS1, BRAF, MET and/or RET*, has been identified in the patient's tumour for the first time. Please refer to the Pathology and Genomics Testing manual for information on targetable alterations in *EGFR, ALK, ROS1, BRAF, MET and RET.*

7.4 Optional re-allocation to different treatment cohort (Modules 1 to 5 only)

From implementation of protocol version 10.0, re-allocation of patients to a different treatment cohort is no longer applicable. The information below relates only to patients who have previously been re-allocated prior to implementation of protocol version 10.0.

Following confirmation of radiological disease progression as per RECIST 1.1, whilst on study, patients in Modules 1 to 5 may be considered for re-allocation to a different treatment cohort (only to Modules 1 to 5 that are actively recruiting). Allocation to an alternative treatment cohort will be informed by molecular testing of the tumour sample acquired prior to first HUDSON treatment and/or at disease progression and by the cohorts open for recruitment at the time of disease progression. A patient must provide informed consent to the second treatment in the HUDSON protocol and must meet the eligibility criteria in the core protocol and re-allocated module prior to study drug administration. A patient may be re-allocated once, that is the patient may receive only one additional protocol treatment.

There should be at least 28 days between the last durvalumab dose of the first HUDSON treatment, and the first dose of the re-allocated HUDSON treatment (please refer to inclusion criterion 5.1.9). Exclusion criterion 5.2.9 will apply for patients who have permanently discontinued durvalumab due to treatment-related toxicity during the first HUDSON treatment. These patients cannot be re-allocated to a second HUDSON treatment where the regimen has durvalumab as part of the combination.

The patient will retain the original enrolment code for the re-enrolment. Vital status will continue to be collected against the first treatment assignment. The SoA during the re-allocation period is summarised in Section 7 in the relevant modules, and will include laboratory safety assessments, AEs and drug administration. The patient will have their original safety follow-up visit scheduled (90 days ±7 days after study treatment discontinuation) unless they have another visit scheduled as part of their re-allocated cohort, that falls within the same time window. In this case, each test or sample that is common to both visits are only required once.

Re-allocation procedure will be as follows:

1 The site informs the local and global AZ teams that the patient would like to be considered for re-allocation to a second treatment within the HUDSON protocol by completing a patient registration form (PRF) and emailing it to the HUDSON mailbox.
2 Global team will confirm where to send the biopsy sample taken on disease progression for biomarker testing.
3 Once all relevant biomarker information is known, patient allocation will proceed.
4 To avoid delay, a patient number will be provided at the time of re-allocation with the clear understanding that **patient must not be dosed if he/she does not meet all the core and module specific eligibility criteria** (excluding inclusion criterion 8 and exclusion criterion 16, which are not applicable to re-allocated patients).
5 Site will then confirm patient dosing date in the PRF.
6 Informed consent and screening period to confirm eligibility criteria for re-allocation will be performed within 28 days of patient being dosed.

Patients who are treated on a second treatment in the HUDSON protocol should continue to be followed for OS.

Up to a maximum of 10 patients may be re-allocated to other modules with each of the different treatments (eg, 10 patients re-allocated to treatment with durvalumab plus olaparib, 10 patients re-allocated to treatment with durvalumab plus AZD6738 etc). This is in addition to the 20 patients already in the treatment cohort.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in the SoA. For all assessments after screening, see the SoA in the specific module.

The investigator will ensure that data are recorded on the eCRFs. The Web Based Data Capture system will be used for data collection and query handling.

The investigator will ensure the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed eCRF. A copy of the completed eCRFs will be archived at the study site.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the patient's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilised for screening or pre-dose purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

8.1 Efficacy assessments

8.1.1 Tumour assessments by CT or MRI scans

RECIST guidelines for measurable, non-measurable, target lesions (TLs) and non-target lesions (NTLs) and the objective tumour response criteria are presented in Appendix G of this CSP.

At baseline, the imaging modalities used for assessment should be contrast enhanced CT (MRI where CT is contraindicated) scans of the chest, abdomen and pelvis (including liver and adrenal glands) and should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients. Follow-up CT or MRI assessments will cover chest, abdomen and pelvis with any other regions imaged at baseline where disease was

present. Any other sites at which new disease is suspected should also be appropriately imaged. A CT/MRI scan of the brain should be performed in all patients at the main screen.

Radiological examinations performed in the conduct of this study should be retained at site as source data. All treatment decisions will be based on site assessment of scans. Duplicates of all radiological examinations (redacted of personal identifiers to the patient) for newly-consented or re-consented patients must be available at the site in readiness to be sent for review, if requested by the Sponsor. Baseline radiological assessments should be performed no more than 28 days before the start of study treatment, and ideally should be performed as close as possible to the start of study treatment. Scans obtained as part of standard clinical practice, prior to informed consent, but within the 28-day period are acceptable. The radiological progression confirmatory scans should be performed no less than 4 weeks after the prior assessment of PD and preferably at the next scheduled visit (in the absence of clinically significant deterioration).

The methods of assessment used at baseline should be used at each subsequent follow-up assessment through to radiologically confirmed disease progression, as defined by RECIST 1.1 and as determined by the investigator. Tumour assessments should be performed every 6 weeks (±1 week) for the first 24 weeks relative to the start of combination therapy (Cycle 1, Day 1), and every 8 weeks (±1 week) (unless otherwise specified in the SoA of the module) thereafter. (Note: More frequent scanning is permitted where this is the local standard), until objective disease progression as defined by RECIST 1.1 and confirmed with a subsequent scan (in the absence of clinically significant deterioration). If a patient discontinues treatment (and/or receives a subsequent cancer therapy) prior to progression then the patient should still continue to be followed (unless they withdraw consent) until confirmed objective disease progression. Scans confirming progression should preferably not be conducted within 1 week of a progression biopsy to allow for reduction in inflammation. Per protocol, scheduled radiological scans will continue for patients with confirmed radiological disease progression and who, in the opinion of the investigator, are still receiving clinical benefit from continuing study treatment. These assessments will continue for as long as the patient is still receiving study treatment (see also Appendix G 4.1).

If scans are performed outside of scheduled visit window interval and the patient has not progressed, every attempt should be made to perform the subsequent scans at their scheduled visits whilst the patient remains on study treatment.

It is important to follow the assessment schedule as closely as possible. Please refer to the study plan in Section 1.1 and the relevant study modules.

8.1.2 Tumour evaluation

RECIST 1.1 will be used to assess patient response to treatment, as assessed by the investigator. The RECIST 1.1 guidelines for measurable, non-measurable, target and NTL and the objective tumour response criteria (complete response [CR], partial response [PR], stable disease [SD] or PD) are presented in Appendix G of this CSP (Eisenhauer et al 2009). In addition to this, a confirmatory scan following objective radiological disease progression will be undertaken (in the absence of clinically significant deterioration).

Categorisation of objective tumour response assessment will be based on the RECIST 1.1 criteria of response: CR, PR, SD and PD. Target lesion progression will be calculated in comparison to when the tumour burden was at a minimum (ie, smallest sum of diameters previously recorded on study). In the absence of progression, tumour response (CR, PR, SD) will be calculated in comparison to the pre-dose tumour measurements obtained before starting treatment.

If the investigator is in doubt as to whether progression has occurred, particularly with response to NTLs or the appearance of a new lesion, it is advisable to continue treatment and reassess the patient's status at the next scheduled assessment or sooner if clinically indicated.

To achieve 'unequivocal progression' on the basis of non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more NTLs is usually not sufficient to qualify for unequivocal disease progression status.

If repeated scans confirm progression, then the date of the initial scan should be declared as the date of progression. All RECIST assessment images will be reviewed at site. Duplicates may be collected and stored by an AstraZeneca appointed representative, and sent for independent central RECIST review, if deemed appropriate.

8.1.2.1 CCI [redacted] for exploratory analysis

CCI [redacted]

may be collected and stored by AstraZeneca or by an AstraZeneca appointed representative for potential review of the exploratory objectives.

CCI [redacted] extracted from each available tumour evaluation image to be measured include, but are not limited to, CCI [redacted] Guidelines for image acquisition, de-identification and transfer to AstraZeneca or to an AstraZeneca appointed representative will be provided.

8.1.3 Survival assessment

8.1.3.1 Dosed patients

Survival status will be obtained for all patients who receive study treatment. Vital status (dead or alive; date of death) will be collected every 3 months (±1 week) after the safety follow-up visit (90 days after study drug discontinuation). If a patient withdraws consent for the safety follow-up visit, but not the survival follow-up, then the first survival follow-up will be collected 3 months (±1 week) after permanent discontinuation of all study treatment. To aid the interpretation of the survival analysis the use of subsequent anti-cancer therapies, after discontinuation of study treatment, will also be recorded on the eCRF. Ad hoc collection of survival status may be requested for OS analyses.

Patients in Modules 1 to 5 re-allocated to a second study treatment will continue to be followed for survival. Survival status will be recorded in the eCRF against the first study treatment, from discontinuation of the first study treatment.

Survival status will continue to be collected until the planned database lock for a module, which can occur either 12 months after the last patient has started treatment or when 75% of the patients have died. The patient does not have to attend the clinic for the assessment to be carried out; it can either be done via a telephone call, or through a review of the patient's notes, or through the use of public records. If the site becomes aware that a patient has died prior to the final analysis, the relevant eCRF on the database should be completed at that time.

8.1.3.2 Screen fail patients

Survival status is not being obtained for screen fail patients who are screened after implementation of protocol version 10.0, as sufficient survival follow-up data for these patients have now been collected (see Section 3). Where screen fail patients have been followed for survival status, vital status (dead or alive; date of death) will be collected every 3 months (±1 week) from the date that the patient is determined to have failed screening until implementation of protocol version 10.0. To aid the interpretation of the survival analysis the use of subsequent anti-cancer therapies will also be recorded on the eCRF.

The patient does not have to attend the clinic for the assessment to be carried out; it can either be done via a telephone call, or through a review of the patient's notes, or through the use of public records. Ad hoc collection of survival status may be requested for OS analyses. If the site becomes aware that a patient has died prior to the final analysis, the relevant eCRF on the database should be completed at that time.

8.2 Safety assessments

Planned time points for all safety assessments are provided in the SoA.

8.2.1 Clinical safety laboratory assessments

See Table 5 for the list of clinical laboratory tests to be performed and refer to the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in the table, must be conducted in accordance with the laboratory manual and the SoA. Results for urea and electrolytes, full blood count, and liver function tests must be available before commencing dosing (within 3 days). All assessments on treatment days are to be performed prior to dosing, unless otherwise indicated.

The investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at the study site as source data for laboratory variables.

Additional safety samples may be collected if clinically indicated at the discretion of the investigator. The date, time of collection, and results (values, units, and reference ranges) will be recorded on the appropriate eCRF.

For information on how AEs based on laboratory tests should be recorded and reported, see Section 8.3.7. All patients who have any CTCAE (v4.03) Grade 3 or 4 laboratory values at the time of completion or discontinuation from study treatment must have further tests performed until the laboratory values have returned to CTCAE Grade 1 or 2, unless these values are not likely to improve because of the underlying disease.

The clinical chemistry, haematology and urinalysis will be performed at a local laboratory at or near the investigator site. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site.

Table 5 Laboratory safety variables

Haematology/Haemostasis (whole blood)	Clinical Chemistry (serum or plasma)
B-Haemoglobin	S/P-Albumin
B-Platelet count	S/P-Alkaline phosphatase (ALP)[a]
B-White blood cell (WBC) count	S/P-Alanine aminotransferase (ALT)[a]
B-Absolute neutrophil count (ANC)[g]	S/P-Amylase[b]
B-Absolute lymphocyte count (ALC)[g]	S/P-Aspartate aminotransferase (AST)[a]
B-Eosinophil count[g]	S/P-Total Calcium
B-Monocyte count[g]	S/P Chloride[c]
B-Red blood cell (RBC) count	S/P-Creatinine clearance[c,f]
B/P-Fibrinogen[e]	S/P-Creatinine
	S/P-Gamma glutamyltransferase[c]
Urinalysis (dipstick)	S/P Glucose (random)
U-Blood	S/P-Lactate dehydrogenase

Table 5 Laboratory safety variables

U-Colour and appearance	S/P-Lipase[b]
U-Ketones	S/P-Magnesium[c]
U-pH	S/P Phosphate
U-Protein	S/P-Potassium
U-Specific gravity	S/P-Sodium
	S/P-Total bilirubin[a]
Coagulation (whole blood or plasma)	S/P-Total protein
B-Activated partial thromboplastin time (APTT)	S/P-TSH
B-International Normalised Ratio (INR)	S/P-T_3 free (reflex)[d]
	S/P-T_4 free (reflex)[d]
	S/P-Urea or BUN, depending on local practice
	S/P-CRP
	S/P-Haptoglobin[e]

[a] Tests for ALT, AST, alkaline phosphatase, and total bilirubin must be conducted and assessed concurrently. If total bilirubin is ≥2 × upper limit of normal (and no evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin.

[b] It is preferable that both amylase and lipase parameters are assessed. For sites where only 1 of these parameters is routinely measured then either lipase or amylase is acceptable.

[c] Bicarbonate (where available), Chloride, Creatinine clearance, gamma glutamyltransferase, magnesium, testing is to be performed at screening, on Day 1 (unless screening laboratory assessments are performed within 3 days prior to Day 1), and if clinically indicated.

[d] Free T_3 or free T_4 will only be measured if TSH is abnormal or if there is a clinical suspicion of an AE related to the endocrine system. As study treatment for Module 11 does not include durvalumab, the evaluation of these parameters is not required.

[e] Haptoglobin and fibrinogen are to be measured approximately monthly for patients treated with durvalumab in combination with AZD9150 (Module 2). More frequent assessments may be performed if clinically indicated

[f] Creatinine clearance to be calculated using the Cockcroft and Gault equation (Cockcroft and Gault 1976). For creatinine values in µmol: Males [(140-age) x weight (kg) x 1.23)]/serum creatinine (µmol/L); Females [(140-age) x weight (kg) x 1.04)]/serum creatinine (µmol/L). For creatinine values in mg/dL: Males [(140-age) x weight (kg)]/[72 x serum creatinine (mgl/dL)]; Females 0.85 x[(140-age) x weight (kg)]/[72 x serum creatinine (mgl/dL)]

[g] Module 3, Module 10 and Module 11 only: Eosinophil, monocyte, lymphocyte and neutrophil counts will be recorded as part of the routine WBC count safety assessment; for Module 3 patients already enrolled at the time of protocol v10.0 in the expanded cohorts and who sign informed consent forms relating to protocol v10.0 or later versions, counts will be recorded retrospectively.

B blood; BUN blood urea nitrogen; CRP C-reactive protein; P plasma; S serum; T_3 triiodothyronine; T_4 thyroxine; TSH thyroid stimulating hormone; U urine; WBC white blood cell.

Note. In case a patient shows an AST **or** ALT ≥3 × ULN together with TBL ≥2 × ULN please refer to Appendix E 'Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law', for further instructions.

8.2.1.1 Coagulation

Activated partial thromboplastin time (APTT) and international normalised ratio (INR) will also be measured at the times specified in the core and module-specific SoA.

The following coagulation variables will be measured:

- APTT will be performed at screening and if clinically indicated
- INR will be performed at screening and if clinically indicated, unless the patient is receiving warfarin

Patients taking warfarin may participate in this study (unless the Module prohibits use); however, it is recommended that prothrombin time (INR and APTT) be monitored carefully at least once per week for the first month, then monthly if the INR is stable.

All coagulation test results will be recorded in the eCRF.

8.2.1.2 Other safety assessments

Pregnancy tests on either urine (human chorionic gonadotropin [hCG]) or blood (serum β-hCG) samples will be performed for pre-menopausal women of childbearing potential as specified in the SoA. Tests will be performed by the local laboratory. If results are positive, the patient must not start or continue treatment. In the event of a suspected pregnancy during the study, the test should be repeated.

Other safety tests to be performed include assessment for hepatitis B surface antigen, hepatitis C antibodies, hepatitis C viral load (for patients with history of hepatitis C only), and HIV antibodies.

8.2.2 Physical examinations

A complete physical examination will be performed at screening and include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculoskeletal (including spine and extremities) and neurological systems. Investigators should pay special attention to clinical signs related to previous serious illnesses. Situations in which physical examination results should be reported as AEs are described in Section 8.3.7.

Height will be measured at screening only. Targeted physical examinations will be performed throughout the treatment period. Assessments will be included at the discretion of the investigator.

8.2.3 Vital signs

Vital signs (blood pressure, pulse rate, temperature, and respiration rate) will be evaluated according to the SoA (see relevant module). Body weight is also recorded at each visit along with vital signs.

- Body temperature, pulse rate, respiratory rate, body weight, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by ≥5 minutes of rest for the patient in a quiet setting without distractions (eg, television, cell phones).

8.2.3.1 Vital signs for study treatments involving durvalumab

For study treatments involving durvalumab, the following applies:

First infusion of durvalumab

On the first day of study drug administration, patients will be monitored and vital signs will be collected/recorded in the eCRF prior to, during, and after infusion of durvalumab as presented in the bulleted list below.

Blood pressure and pulse rate will be collected from patients prior to, during, and after each infusion at the following times (based on a 60-minute infusion):

- Prior to the beginning of each infusion (measured once from approximately 30 minutes before up to 0 minutes [ie, the beginning of the infusion])
- Approximately 30 minutes during the infusion (halfway through infusion)
- At the end of the infusion (after approximately 60 minutes ± 15 minutes)
- A 1-hour observation period is recommended after the first infusion of durvalumab. If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be at the investigator's discretion (suggested 30 minutes after each durvalumab infusion).

If the infusion takes longer than 60 minutes, then BP and pulse rate measurements should follow the principles as described above or be taken more frequently if clinically indicated. A 1-hour observation period is recommended after the first infusion of durvalumab. Additional monitoring with assessment of vital signs will be at the discretion of the investigator per standard clinical practice or as clinically indicated.

Subsequent infusions

BP, pulse rate, and other vital signs should be measured and collected/recorded in the eCRF prior to the start of the infusion. Patients should be carefully monitored, and BP and other

vital signs should be measured during and after infusion as per institution standard and as clinically indicated. Any clinically significant changes in vital signs should be entered onto the vital signs eCRF.

Any changes in vital signs should be recorded as an AE (if applicable). For information on how AEs based on changes in vital signs should be recorded as an AE, see Section 8.3.7.

8.2.4 Electrocardiograms

- 12-lead ECG will be obtained as outlined in the SoA (see Section 1.1) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, and QT intervals.
- At screening, and for each on-study time point, triplicate ECGs should be taken as per the SoA in each module.
- At each time point, 3 individual ECG tracings should be obtained in succession, no more than 2 minutes apart. The full set of triplicates should be completed within 5 minutes.
- ECGs will be obtained after the patient has been resting. All ECGs should be recorded with the patient in the same physical position. A standardised ECG machine should be used and the patient should be examined using the same machine throughout the study, where feasible.
- After ECGs have been recorded, the investigator or designated physician will review each of the ECGs and may refer to a local cardiologist if appropriate. A paper copy should be filed in the patient's medical records. If an abnormal ECG finding at screening or pre-dose is considered to be clinically significant by the investigator, it should be reported as a concurrent condition. For all ECGs details of rhythm, ECG intervals and an overall evaluation will be recorded. Any clinically significant abnormalities detected require a confirmatory ECG. In case of clinically significant ECG abnormalities including an ECG that demonstrates a QTcF value >500 msec, 2 additional 12-lead ECGs should be obtained over a brief period (eg, 30 minutes) to confirm prolongation based on the average QTcF value manually over-read by a medically qualified person.
- A proportion of ECG data may also be collected digitally and may be transferred electronically for central analysis as described in the study-specific ECG manual (if applicable). Heart rate, PR, R-R, QRS and QT intervals may be determined and reviewed by an external cardiologist.

8.2.5 Performance status

The patient's performance status will be assessed at screening using the ECOG/WHO Performance Status scale. Patients must have an ECOG/WHO performance status 0 to 1 to be eligible for enrolment.

These scales and criteria are used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis (Oken et al 1982, see Table 6).

Table 6 Eastern Cooperative Oncology Group performance status

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

8.3 Collection of adverse events

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section

The definitions of an AE or SAE can be found in Appendix B.

An AE will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorised representative).

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. For information on how to follow/up AEs see section 8.3.3.

All confirmed or suspected COVID-19 infection events must be recorded in the eCRF.

8.3.1 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

8.3.2 Time period and frequency for collecting AE and SAE information

Adverse events will be collected from the time of signature of the pre-screen ICF throughout the treatment period and including the safety follow-up (90 days after the discontinuation of all study drugs or until initiation of another therapy, unless the investigator assesses that the event occurring within 90 days after last dose of study treatment but after the initiation of another therapy, is related to the study treatment).

Procedure related AEs and SAEs only will be captured from the time of signature of the pre-screen informed consent for those patients who provide a new tumour biopsy. AEs and

SAEs occurring up to and including 21 days after the new tumour biopsy procedure will be recorded.

All SAEs will be recorded from the time of signing of the main screening informed consent.

For patients who continue to receive intervention after final database lock, investigators will continue to report all non-serious AEs and SAEs to AstraZeneca Patient Safety until 90 days after study intervention is discontinued (see Section 4.4).

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Section 8.4.1. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE in former study patients. However, if the investigator learns of any SAE, including a death, at any time after a patient's last visit and he/she considers the event to be reasonably related to the Study treatment or study participation, the investigator may notify the sponsor.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each patient at subsequent visits/contacts. All SAEs/non-serious AEs/AEs of special interest, will be followed until resolution, stabilisation, the event is otherwise explained, or the patient is lost to follow-up. Please refer to each specific module for guidance regarding AEs of special interest. For re-allocated patients (Modules 1 to 5 only), AE follow-up will occur up to the day prior to the start of the second treatment.

Any AEs that are unresolved at the patient's last AE assessment or other assessment/visit as appropriate in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

8.3.4 Adverse event data collection

'The following variables will be collected for each AE:

- AE (verbatim)
- The date and time when the AE started and stopped
- The CTCAE grade and grade changes, with the date they changed
- Whether the AE is serious or not
- Whether the AE is of special interest or not
- Whether the AE is an infusion reaction (yes or no)

- Investigator causality rating against the study treatment (yes or no)
- Action taken with regard to study treatment
- AE caused patient's withdrawal from study (yes/no)
- Administration of treatment for the AE
- Outcome.

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date investigator became aware of SAE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication
- Description of AE.

8.3.5 Causality collection

The investigator will assess causal relationship between study drug and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the study drug?'.

For SAEs, causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B to the CSP.

8.3.6 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study site staff: 'Have you had any health problems since the previous visit/you were last asked?', or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.3.7 Adverse events based on examinations and tests

The results from the CSP-mandated laboratory tests and vital signs will be summarised in the clinical study report (CSR). Deterioration as compared to pre-dose in protocol-mandated targeted physical examination, vital signs, and clinical safety laboratory values, should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the study drug, or are considered to be clinically relevant as judged by the investigator (which may include but not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study treatment, eg, dose adjustment or drug interruption).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the pre-dose assessment will be reported as an AE.

8.3.8 Hy's Law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥3 × ULN together with TBL ≥2 × ULN may need to be reported as SAEs unless related to the underlying disease. Please refer to Appendix E for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law (HL).

8.3.9 Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the study drug is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of symptoms consistent with disease progression, or, the development of new, or progression of existing metastasis to the primary cancer under study, should be considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

8.3.10 New cancers

The development of a new cancer should be regarded as an SAE. New primary cancers are those that are not the primary reason for the administration of the study drug and have been identified after the patient's inclusion in this study.

8.3.11 Deaths

All deaths that occur during the study treatment period, or within the protocol-defined follow-up period after the administration of the last dose of study drug, must be reported as follows:

- Death clearly resulting from disease progression should be documented in the eCRF in the Statement of Death page. It should not be reported as an SAE.
- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to the study physician as an SAE within 24 hours. It should also be documented in the Statement of Death page in the eCRF. The report should contain a comment regarding the co-involvement of PD, if appropriate, and should assign main and contributory causes of death.
- Deaths with an unknown cause should always be reported as an SAE. It should also be documented in the Statement of Death page in the eCRF. A post-mortem may be helpful in the assessment of the cause of death, and if performed, a copy of the post-mortem results should be forwarded to AstraZeneca Patient Safety or its representative within the usual timeframes.

Deaths occurring after the protocol defined safety follow-up period after the administration of the last dose of study drug should be documented in the Statement of Death page. If the death occurred as a result of an event that started post the defined safety follow-up period and the event is considered to be due to a late onset toxicity to study drug, then it should also be reported as an SAE.

8.3.12 Adverse events of special interest

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the study drug and may require close monitoring. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterise and understand them in association with the use of this study drug.

Durvalumab

Adverse events of special interest for durvalumab include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants and/or hormone replacement therapy. These AESIs are being closely monitored in clinical studies with durvalumab monotherapy and combination therapy. An immune-mediated adverse event

(imAE) is defined as an AESI that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate aetiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other aetiologic causes of the imAE.

If the investigator has any questions about an event being an imAE, the investigator should promptly contact the study physician.

AESIs observed with durvalumab include:

- Diarrhoea/colitis and intestinal perforation
- Pneumonitis/interstitial lung disease (ILD)
- Endocrinopathies (ie, events of thyroiditis, hypophysitis/hypopituitarism, adrenal insufficiency, hyper- and hypo-thyroidism and type I diabetes mellitus)
- Hepatitis/transaminase increases
- Nephritis/blood creatinine increases
- Pancreatitis/serum lipase and amylase increases
- Rash/dermatitis
- Myocarditis
- Myositis/polymyositis
- Neuropathy/neuromuscular toxicity (eg, Guillain-Barré, and myasthenia gravis)
- Uveitis
- Immune-mediated arthritis
- Other inflammatory responses that are rare/less frequent with a potential immune-mediated aetiology include, but are not limited to, pericarditis, sarcoidosis, other events involving the eye, skin, haematological, and rheumatological events, vasculitis, non-infectious meningitis and non-infectious encephalitis.

In addition, infusion-related reactions and hypersensitivity/anaphylactic reactions with a different underlying pharmacological aetiology are also considered AESIs.

Further information on these risks (eg, presenting symptoms) can be found in the current version of the durvalumab IB. More specific guidelines for their evaluation and treatment are described in detail in the Dosing Modification and Toxicity Management Guidelines (see Section 8.4.5). These guidelines have been prepared by the sponsor to assist the investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to the study drug/study regimen by the reporting investigator.

Combination drug products

AESIs for the drug products to be administered as monotherapy or in combination with durvalumab are described in the individual modules and current IBs.

8.3.13 Safety data to be collected following the database lock of each module

For patients continuing to receive treatment after database lock of each module, it is recommended that the patients continue the scheduled site visits and Investigators monitor the patient's safety laboratory results prior to and periodically during treatment in order to manage AEs in accordance with the durvalumab Dose Modification and Toxicity Management Guidelines (see Section 8.4.5) and the specific toxicity management guidelines for each study drug as described in appropriate module. All data post database lock for each module will be recorded in the patient notes but, with the exception of non-serious AEs and SAEs, will not otherwise be reported for the purposes of this study.

All non-serious AEs and SAEs that occur in patients still receiving treatment (or within the 90 days following the last dose of treatment) post the database lock for each module must be reported as detailed in Section 8.4.1.

8.3.14 Continued access to study intervention after the end of the study

AstraZeneca will continue to supply study treatment to patients after final database lock while, in the opinion of the Investigator, the participant is benefiting. Patients should be followed according to institution's standard of care assessments or accordance with standard local clinical practice. No further data collection is required except reporting of AEs, SAEs, AESIs, overdoses, pregnancies, medication error, drug abuse and drug misuse.

In the event that product development reaches a point where alternative product supply options become available, then these alternative product supply options will be discussed by AstraZeneca with the Investigator. AstraZeneca will work with the Investigator to transition the patient(s) to alternative supply, unless impossible for local reasons.

In the event that a roll-over or safety extension study is available, patient(s) currently receiving treatment may then be transitioned to such a study, and the current study may reach its end. The roll-over or extension study would ensure treatment continuation with visit assessments per its protocol, as applicable. Any patient who would be eligible to move to such a study would be given a new informed consent, as applicable.

In the event that AstraZeneca terminates further development of the study intervention, AstraZeneca will continue to supply study intervention where possible, however the supply may become unavailable. AstraZeneca will notify Investigators in advance if supply of study intervention must be discontinued.

8.4 Safety reporting and medical management

8.4.1 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the study treatment, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, then investigators or other site personnel inform the appropriate AstraZeneca representatives within 1 day ie, immediately but **no later than 24 hours** of when he/she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site (AZ DES) **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within 1 calendar day ie, immediately but **no later than 24 hours** of when he/she becomes aware of it.

Once the investigators or other site personnel indicate an AE is serious in the electronic data capture (EDC) system, an automated email alert is sent to the designated AstraZeneca representative.

If the EDC system is not available, then the investigator or other study site staff reports a SAE to the appropriate AstraZeneca representative by telephone followed by completion of a paper SAE form. The AstraZeneca representative will advise the investigator/study site staff how to proceed.

The AstraZeneca representative will advise the investigator/study site staff how to proceed.

In the European Union, the Sponsor will comply with safety reporting requirements and procedures as described in the European Clinical Trials Regulation (EU) No 536/2014. All Suspected Unexpected Serious Adverse Reactions (SUSARs) to the investigational medicinal product will be reported to the EudraVigilance database within the required regulatory timelines.

Non-serious AEs and SAEs will be recorded by the treating physician from the time the patient signs informed consent and will continue throughout the program until the end of the post-trial access period or until consent has been withdrawn. Reports of pregnancy, overdose, medication error, drug abuse, and drug misuse with associated non-serious AEs and SAEs will be reported to the AZ DES within the same timelines specified for SAEs.

For further guidance on the definition of a SAE, see Appendix B of the CSP.

8.4.2 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- If the pregnancy is discovered before the study patient has received any study drug.

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy.

Abnormal pregnancy outcomes (eg, spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.4.2.1 Maternal exposure

If a patient becomes pregnant during the course of the study, study treatment should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study drug under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day ie, immediately but **no later than 24 hours** of when he/she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AZ DES within 1 or 5 calendar days for SAEs (see Section 8.4.1) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

8.4.2.2 Paternal exposure

Information on the pregnancy of a patient's partner must be obtained directly from the patient's partner. Therefore, prior to obtaining information on the pregnancy, the investigator must obtain the consent of the patient's partner.

Male patients must refrain from fathering a child or donating sperm during the study and for 6 months following the last dose of study treatment.

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should, if possible, be followed up and documented. To capture information about a pregnancy from the partner of a male patient, consent must be obtained from the male patient's partner in order to collect information related to the pregnancy and outcome; the male patient should not be asked to provide this information. A consent form specific to this situation must be used.

The outcome of any conception occurring from the date of the first dose until 6 months after the last dose of study treatment should be followed up and documented.

8.4.3 Overdose

For this study, any dose of durvalumab or any other agent studied in doses in excess of those specified in the protocol is considered to be an overdose. There is currently no specific treatment in the event of overdose of durvalumab or any other agent studied; therefore, possible symptoms of overdose are not established.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then the investigator or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he/she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AZ DES.

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 8.4.1. For other overdoses, reporting must occur within 30 days.

8.4.4 Medication error, drug abuse, and drug misuse

8.4.4.1 Timelines

If an event of medication error, drug abuse **or** drug misuse occurs in the course of the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within **one calendar day** ie, immediately but **no later than 24 hours** of when he/she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is completed within **one** (initial fatal/life-threatening or follow-up fatal/life-threatening) **or 5** (other serious initial and follow-up) **calendar days** if there is an SAE associated with the medication error, drug abuse, or misuse (see Section 8.4.1) and **within 30 days** for all other events.

8.4.4.2 Medication error

For the purposes of this clinical study a medication error is an **unintended** failure or mistake in the treatment process for an AstraZeneca study drug that either causes harm to the patient or has the potential to cause harm to the patient.

The full definition and examples of a medication error can be found in Appendix B.

8.4.4.3 Drug abuse

Drug abuse is the persistent or sporadic **intentional**, non-therapeutic excessive use an AstraZeneca study drug for a perceived reward or desired non-therapeutic effect.

The full definition and examples of drug abuse can be found in Appendix B.

8.4.4.4 Drug misuse

Drug misuse is the **intentional** and inappropriate use (by a study patient) of an AstraZeneca study drug for medicinal purposes outside of the authorised product information, or for unauthorised AstraZeneca study drugs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

The full definition and examples of drug misuse can be found in Appendix B.

8.4.5 Management of study drug-related toxicities

The following general guidance should be followed for management of toxicities.

- Treat each of the toxicities with maximum supportive care (including withholding the agent suspected of causing the toxicity if required).
- If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of the assigned investigational product along with appropriate continuing supportive care. If medically appropriate, dose modifications are permitted.
- All dose modifications should be documented with clear reasoning and documentation of the approach taken.

All toxicities will be graded according to NCI CTCAE, version 4.03.

Guidelines for the management of immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions for durvalumab monotherapy and durvalumab combination

therapies are provided in the Dosing Modifications and Toxicity Management Guidelines. The most current version of these guidelines is to be maintained within the Site Master File.

The management of other study drug-related toxicities is provided in the relevant module.

8.5 Pharmacokinetics

Blood samples will be collected for measurement of serum or plasma concentrations of AZD9150 for Module 2 (durvalumab plus AZD9150), for both study drugs in Module 6 (durvalumab plus trastuzumab deruxtecan), for cediranib in Module 7 (durvalumab plus cediranib), and for both study drugs in Module 10 (durvalumab plus AZD6738), as specified below. There will be no pharmacokinetic (PK) measurements in the other modules. The collection of samples for PK analysis may be stopped or reduced if it is determined that no further useful information can be gained from collecting these samples. The actual date and time (24-hour clock time) of each sample will be recorded.

The total volume of blood taken from each patient will not exceed that described in Section 8.8.8.1.

Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

Module 2

Pharmacokinetic samples will be taken on the days shown in Table 7.

Table 7 AZD9150 PK blood sample schedule for patients receiving durvalumab plus AZD9150

Time relative to dose	Cycle 0 Day 1	Cycle 0 Day 5	Cycle 1 Day 15	Cycle 2 Day 1	Cycle 4 Day 1	Study drug discontinuation
Pre- and post-dose of AZD9150[a]	X	X	X	X	X	
During visit						X

[a] PK samples are to be taken prior to infusions (up to 2 hours pre-dose) and 1 hour after AZD9150 infusion (post-dose, prior to durvalumab infusion) except on the study drug discontinuation visit

On days where durvalumab and AZD9150 infusions occur, the end of infusion sample is to be collected at the end of the AZD9150 infusion (not after the durvalumab infusion).

Module 6

Pharmacokinetic samples will be taken on the days shown in Table 8. For patients who receive chloroquine or hydroxychloroquine, additional PK blood draws will be taken at the following timepoints during the chloroquine/hydroxychloroquine treatment period:

- before the first dose of chloroquine/hydroxychloroquine dosing,
- before chloroquine/hydroxychloroquine dosing on Day 3 or 4,
- on the last day of chloroquine/hydroxychloroquine treatment,
- pre-dose on the day of restarting trastuzumab deruxtecan treatment, if trastuzumab deruxtecan is restarted.

Following these blood PK draws, if trastuzumab deruxtecan is restarted, routine trastuzumab deruxtecan PK blood sample collection will continue as per the schedule.

Table 8 Durvalumab and trastuzumab deruxtecan PK blood sample schedule

Time relative to dose	Cycle 1 Day 1	Cycle 2 Day 1	Cycle 4 Day 1	Study drug discontinuation During visit
Durvalumab[a]	X[a]	X[a]	X[a]	X
Trastuzumab deruxtecan[b]	X[b]	X[c]	X[c]	X

[a] PK samples are to be taken prior to the infusion of trastuzumab deruxtecan (up to 2 hours pre-dose)
[b] PK samples are to be taken prior to the infusion of trastuzumab deruxtecan (up to 2 hours pre-dose), within 15 minutes after infusion of trastuzumab deruxtecan, and 5 hours after infusion of trastuzumab deruxtecan (±2 hours post dose)
[c] PK samples are to be taken prior to the infusion of trastuzumab deruxtecan (up to 2 hours pre-dose), and within 15 minutes after infusion of trastuzumab deruxtecan

Module 7

PK samples will be taken on the days shown in Table 9.

Table 9 Cediranib PK blood sample schedule for patients receiving durvalumab plus cediranib

Time relative to dose	Cycle 2 Day 1	Cycle 4 Day 1
Pre-dose of cediranib	X	X
2 hours post-dose of cediranib	X	X

Module 10

Pharmacokinetic samples will be taken on the days shown in Table 10 and Table 11.

Table 10 AZD6738 PK plasma sample schedule for patients receiving durvalumab plus AZD6738

Time relative to dose	Cycle 0		Cycles 1, 2, 3, 4, 8 and 12	
	D1	D7[c]	D22	D28[c]
Pre-dose[a]		X		X
Post-dose	X[b]	X	X[b]	X

[a] Pre-dose samples within 1 hour (± 10 minutes) before the AZD6738 dose.
[b] Post-dose samples at 1 hour (± 10 minutes) after the AZD6738 dose. Cycle 0 Day 1 post-dose sample should be taken at 1 hour (± 10 minutes) after the morning AZD6738 dose.
[c] On Day 7 of Cycle 0 and on Day 28 (Cycle 1 onwards), samples can be taken either pre-dose and post-dose of the morning AZD6738 dose OR pre-dose and post-dose of the evening AZD6738 dose, a -2-day window being allowed.

Table 11 Durvalumab PK sample schedule for patients receiving durvalumab plus AZD6738

Time relative to dose	Cycle 1 Day 1	Cycles 2, 4, 8 and 12 Day 1	Safety Follow-up 90 days after study drug discontinuation
Pre-dose[a]	X		
Post-dose[a]	X	X	X

[a] Pre-dose sample (Cycle 1 Day 1) to be taken within 1 hour (± 10 minutes) before the start of infusion. Post-dose samples (excluding safety follow-up sample) to be taken at the end of durvalumab infusion (or within 10 minutes from the end of infusion). Samples should be taken from the arm opposite to the arm where durvalumab infusion is administered.

8.5.1 Determination of drug concentration

Samples for determination of drug concentration in serum or plasma will be analysed by an approved laboratory vendor as required on behalf of AstraZeneca, using an appropriate bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

In addition, the PK samples may be subjected to further analyses (when applicable) in order to further investigate the presence and/or identity of drug metabolites. Any results from such analyses will be reported separately from the CSR.

8.5.2 Storage and destruction of pharmacokinetic samples

Pharmacokinetic samples will be disposed of after the Bioanalytical Report finalisation or six months after issuance of the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses.

Pharmacokinetic samples may be disposed of or destroyed and anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

8.5.3 Other assessments – anti-drug antibody samples

Presence of anti-drug antibodies (ADA) for durvalumab will be assessed in samples from those patients receiving durvalumab treatment in any study module according to the schedule presented in Table 12 and Table 13. In addition, presence of ADA for trastuzumab deruxtecan

will be assessed in samples from those patients receiving trastuzumab deruxtecan treatment in Module 6.

Table 12 ADA blood sample schedule for durvalumab and trastuzumab deruxtecan

Time relative to dose	Cycle 1	Cycle 2	Cycle 5	90-day follow-up
	Day 1	Day 1	Day 1	
Modules 1, 2, 3, 4, 5, 7, and 9: pre-dose of durvalumab **Module 6:** pre-dose of trastuzumab deruxtecan	X	X[a]	X then Q12W in first year, then Q24W in second year	
During visit				X

[a] In Module 2, the sample should be taken pre-dose of AZD9150 (per Table 14).
ADA anti-drug antibodies; Q12W every 12 weeks; Q24W every 24 weeks.

Table 13 ADA blood sample schedule for durvalumab (for Module 10 only)

Time relative to dose	Cycle 1	Cycle 2	Cycle 4	Cycle 8	Cycle 12	90-day follow-up
	Day 1	Day 1	Day 1	Day 1	Day 1	
Pre-dose[a] of durvalumab	**X**	**X**	**X**	**X**	**X**	**X**

[a] Except at 90-day follow-up.
ADA anti-drug antibodies.

In addition, ADA samples will be analysed for AZD9150 in Module 2. Samples will be taken at the timepoints shown in Table 14.

Table 14 ADA blood sample schedule for AZD9150 (for Module 2 only)

Time relative to dose	Cycle 0	Cycle 0	Cycle 1	Cycle 2	Cycle 4	Study drug discontinuation
	Day 1	Day 5	Day 15	Day 1	Day 1	
Pre-dose of AZD9150	X	X	X	X	X	
During visit						X

ADA anti-drug antibodies

Samples will be measured for the presence of ADA using validated assays.

8.6 Pharmacodynamics

Pharmacodynamic parameters will be evaluated in Modules 3, 8, 9, 10 and 11 of this study. Samples will be analysed, amongst others, for downstream effects on the ATR or related

pathways that may include but not limited to biomarkers pRAD50 and γ-H2AX markers such as lymphocytic infiltration (TILs), PD-L1, and T-cell receptor repertoire; small molecules including ceralasertib, and cytokines may also be assessed. Where feasible, the same approach will be conducted for other modules in this study.

8.7 Genetics

8.7.1 Optional exploratory CCI sample

A CCI blood sample for CCI will be collected from patients who have consented to participate in the genetic analysis component of the study. Participation is optional. Patients who do not wish to participate in the genetic research may still participate in the study.

In the event of CCI failure, a replacement CCI may be requested from the patient. A signed ICF will be required to obtain a replacement sample unless it was included in the original ICF.

See Appendix D for Information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in Appendix D or in the Laboratory Manual.

8.7.2 Storage and destruction of genetic samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. Samples will be stored for a maximum of 15 years or as per local regulations from the date of the Last Patient's Last Visit, after which they will be destroyed. DNA is a finite resource that may be used up during analyses. The results of the genetic analyses will be reported in peer-reviewed journals.

No personal details identifying the individual will be available to AstraZeneca or designated organisations working with the DNA.

8.8 Biomarkers

The patient's consent to the use of donated biological samples is mandatory.

At screening patients are required to consent to 2 mandatory provisions of tissue, 1 new biopsy during screening and 1 on-treatment at 6 ±2 weeks. For Module 10 and Module 11 only, if in agreement with the sponsor study physician, patients may be exempt from requiring a tumour biopsy at pre-screening if a tissue sample is obtained post-progression on prior anti-PD-(L)1 therapy and ≤ 3 months prior to pre-screening. Where no such sample is available, a tumour sample taken after progression on anti-PD-(L)1 therapy and within the previous 24 months is acceptable. There is 1 subsequent mandatory provision of tissue at progression only for patients in Modules 1 to 5 for re-allocation to a second study treatment.

- MANDATORY: Provision of a tumour biopsy that is formalin-fixed and embedded in paraffin. A newly acquired tumour biopsy is strongly preferred; however, if not clinically feasible, a recent sample within approximately 3 months of main-screen consent (or for Module 10 and Module 11 only, as described above, if in agreement with the sponsor study physician) may be submitted.
- MANDATORY: The collection of additional archived tumour tissue block (formalin-fixed and paraffin-embedded) is mandated, where such samples exist in a quantity sufficient to allow for analysis and is strongly encouraged for all patients. Tumour tissue block is preferred. If a tissue block is unavailable, unstained sections from the tissue block may be submitted. Please consult the Laboratory Manual for specific instructions and guidelines regarding sections.
- MANDATORY: Provision of an on-treatment biopsy, at 6 weeks (±2 weeks) from Cycle 1, Day 1. Required for all patients unless clinically contraindicated. Provision of an on-treatment biopsy is not required if a fresh tumour sample is not collected at pre-screening.
- MANDATORY: Provision of tumour biopsies at the time of progression prior to re-allocation to a second study treatment is mandated (Modules 1 to 5 only).
- OPTIONAL: Provision of biopsies upon progression is strongly encouraged for all patients in all modules. Not required if a fresh tumour sample is not collected at pre-screening.
- MANDATORY: Provision of a blood sample for the analysis of molecular profile. This may be used for prospective patient allocation on the availability of a validated central test in a CLIA laboratory.

Biological samples (eg, archived or new tumour biopsy, blood, plasma, serum) will be collected as detailed in the Laboratory Manual for the reasons listed below:

(a) To carry out prospective screening and retrospective biomarker analysis

(b) To analyse exploratory biomarkers to assess correlations with disease activity, effects of study drug, and clinical outcomes

(c) Alternative biomarkers may be evaluated as determined by additional data associated with disease progression or response to study drugs studied under this protocol

(d) To explore the feasibility of reliably identifying predictive biomarkers and to enable future diagnostic development.

Biomarker assessments that may have the potential to identify patients likely to respond to treatment with the agents studied in this modular protocol will be investigated to determine a patient's biomarker status and for possible correlation with efficacy endpoints. Biomarker data may also support subsequent treatment with additional targeted agents and/or combinations.

The results may be pooled with biomarker data from other studies to test existing hypotheses or to generate hypotheses to be tested in future studies with the agents studied.

Samples will be taken at the times shown in the SoA in the relevant appendices.

8.8.1 Collection of tumour samples for biomarker assessments

Archival (if available) and newly collected tumour samples are mandated for the study, unless otherwise stated (see specific module). Biomarker assessments will include, but not be limited to, the pre-defined biomarkers that determine eligibility for the study. New tumour biopsies will be collected from patients who have accessible tumours after the patient's consent has been obtained.

The tumour specimen submitted to establish eligibility should be of sufficient quality and quantity to allow for next generation sequencing (NGS) and IHC analyses (see the Laboratory Manual). Newly acquired, or archived specimens with insufficient tumour content, or fine needle aspirates, are inadequate to establish patient eligibility or to meet the protocol-defined exploratory objectives.

Details of sample collection, processing, shipping, and storage will be described in the Laboratory Manual and/or the Pathology and Genomic Testing manual.

8.8.1.1 Collection of archival tumour samples

Archival (>3 months old) formalin-fixed tumour tissue embedded in paraffin blocks are to be retrieved for all patients if available for pre-screen molecular profiling. The archival samples are preferably from the primary tumour and/or metastatic site. Because uncontrolled oxidation processes affect tumour sections, tumour tissue blocks are preferred (please refer to the Pathology and Genomic Testing Manual for details about sample processing). Freshly prepared unstained sections from the archival formalin-fixed paraffin embedded (FFPE) tumour block are acceptable (minimum of 20 sections), if tumour blocks cannot be submitted.

Archival tumour samples collected to establish eligibility and determine cohort allocation should be sent to the testing laboratories, as detailed in the Laboratory Manual.

An archival tumour sample does not substitute for the newly collected pre-dose tumour sample for biomarker analyses (see Section 8.8.1.2).

8.8.1.2 Collection of new tumour samples

New tumour biopsies are mandatory for all patients after the patient's consent has been obtained, unless otherwise stated (see specific module). The newly collected pre-dose tumour sample will be used to evaluate the biomarker status of the tumour via prospective or retrospective analysis (1) to establish eligibility and cohort allocation (if not already established using pre-existing data or an archival tumour sample), and (2) for protocol-defined

exploratory objectives. All subsequent newly collected tumour samples will be used for protocol-defined exploratory objectives.

Newly collected biopsy samples will be used for NGS analysis of the specific tumour mutation status, overall tumour mutational burden, as well as for gene expression (immune status) and expression of proteins of interest by IHC. Protein markers will include but are not limited to ATM and PD-L1.

When fresh tissue is obtained, effort should be made to maximise material for downstream analyses. As guidance, it is anticipated that 4 passes of a core needle will provide sufficient tissue for establishing eligibility and for delivering protocol-defined exploratory objectives. Multiple cores will be provided for freezing and formalin fixing.

At each time point, new tumour biopsies will be collected (minimum of 4 cores); 1 core will be frozen whenever feasible (1 sample) and ≥3 cores will be FFPE in each block. Please consult the Pathology and Genomic Testing Manual for additional information and guidance regarding how to split excisional biopsies for downstream purposes. Biopsies should be reviewed for presence, quantity, quality, and histologic type of tumour tissue by the dedicated local pathologist.

Tumour lesions used for new biopsies should not be the same lesions used as RECIST TLs, unless there are no other lesions suitable for biopsy. If a RECIST target lesion (TL) is used for biopsy, the lesion must be ≥2 cm in the longest diameter and must be biopsied outside of the main screening period.

If possible, sites should collect pre- and on-treatment biopsies from the same tumour lesion. Accessible lesions are defined as tumour lesions that can be biopsied and that are amenable to repeat biopsy.

An on-treatment tumour biopsy is required for all patients at 6 weeks (±2 weeks) unless clinically contraindicated in the opinion of the investigator, or if a fresh tumour sample is not collected at pre-screening. The on-treatment biopsy may be taken at a later time point with agreement of the study team. Details for processing, handling, and shipping are in the Laboratory Manual.

A new tumour biopsy at disease progression is encouraged for all patients and is mandatory for patients in Modules 1 to 5 who are to be screened for re-allocation to a second treatment cohort. This sample will be used to investigate changes in pathway signalling and potential mechanisms of resistance (ie, genetic alterations, or evidence of alternative pathway activation).

Biopsies at disease progression are optional in this study, and participants will not be excluded from the study if these samples are not collected. Biopsies on disease progression may be particularly valuable when there is a marked phenotypic change in a particular lesion, and investigators are encouraged to contact the sponsor in these cases. The provision of tumour tissue is encouraged only if clinically appropriate and not considered detrimental to participant care.

Sampling should be undertaken by experienced physicians in appropriate medical facilities in accordance with standard clinical practice of patients with advanced NSCLC. Where possible, high-risk sites (such as brain, pancreas etc.) will be avoided.

Details of sample collection, processing, shipping, and storage will be described in the Laboratory Manual.

8.8.2 Collection of plasma samples of CCI

Blood samples will be collected to provide plasma for CCI, for the exploratory analysis of predictive biomarkers to enable future diagnostic development, and to interrogate changes in genetic alterations and potential mechanisms of resistance. Where available, plasma CCI from these samples may also be used for patient allocation.

Samples will be processed to generate CCI and in some instances CCI and where isolated, CCI will be used for the quantitation and profiling of ctDNA through sequencing, assessment of methylation, or other appropriate analysis.

Samples will be collected before and during the treatment period, and at discontinuation, for measurement of mutation status and changes in mutant allelic fraction as measure of response, and for the purpose of exploring the potential of determining predictive biomarker alterations via analysis of CCI to enable future diagnostic development. The results of this exploratory research will be reported separately and will not form part of the CSR.

Details of sample collection, processing, shipping and storage will be described in the Laboratory Manual.

8.8.3 Collection of blood samples to assess immune status

Blood samples, including whole blood, whole blood for peripheral blood mononuclear cells, plasma or serum, will be taken at multiple time points and analysed for a range of oncology and immunological biomarkers that may correlate with drug response. These biomarkers include, but are not limited to activated T cells, effector CD8 T-cells, T cell receptor (TCR) repertoire, CCI and cytokines.

Whole blood for gene expression will be taken for isolation of circulating RNA. Isolated RNA will be used for analysis including, but not limited to, quantifying the expression of specific

genes or gene signatures before and after treatment, as well as assessment of their relationship to outcome following treatment.

Whole blood to extract plasma and serum will be collected from all participants as described in the SoA. Plasma and serum will be used for analysis of blood-based biomarkers including, but not limited to, quantification of circulating proteins.

Whole blood will be taken for flow cytometric measurements of immune cell status. Serum and plasma cytokines to be measured for immune status include but are not limited to CCI

Sequencing of isolated DNA may include targeted sequencing of T cell and B cell receptor sequences, in order to assess the diversity of baseline and on treatment immune responses and targeted sequencing of the CCI The TCR repertoire measurements to be measured include but are not limited to clonality and diversity.

Timings for collection of blood samples for this research are presented in the SoA. The results of this exploratory research will be reported separately and will not form part of the CSR.

Details on sample collection, processing, handling, shipment, and storage are provided in the Laboratory Manual.

8.8.4 Management of biomarker data

The biomarker data will have exploratory significance only. AstraZeneca will not provide biomarker research results to patients, their family members, any insurance company, an employer, general physician or any other third party, unless required to do so by law.

The biomarker status (positive, negative or unknown) of qualifying molecular aberrations will be reported to the investigator as part of the clinical trial report. Furthermore, the clinical investigator may also request access to the panel of molecular data generated at the central laboratory, at a later date (eg, following patient discontinuation). The patient's biomarker data will not be used for any purpose other than those described in the ICF.

Individual patients will not be identified in any report or publication resulting from this work. The data and results of this research may be reviewed with collaborators and published, but neither the patient's name nor any other personal identifiers will appear in any publication or report.

8.8.5 Labelling and shipment of biological samples

The investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix C'IATA 6.2 Guidance Document'.

Any samples identified as Infectious Category A materials are not shipped and no further samples will be taken from the patient unless agreed with AstraZeneca and appropriate labelling, shipment and containment provisions are approved.

8.8.6 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle, details can be found in Appendix C.

8.8.7 Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

The Principal Investigator:

- Ensures that the withdrawal of consent checklist is completed with the patient and the data are also entered into the study database
- Ensures patients' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of/destroyed, and the action documented
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the signed document returned to the study site. Archival tissue blocks can be repatriated on request
- Ensures that the patient and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the central laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

AstraZeneca ensures that biological samples are returned to the source or destroyed at the end of a specified period as described in the informed consent.

8.8.8 Biological sampling procedures

8.8.8.1 Volume of blood

The number of samples taken, as well as the volume required for each analysis, may be changed during the study as emerging data become available. However, the estimated total volume of blood that will be drawn from each patient in this study during screening and the first cycle of treatment will not exceed 300 mL (over a 1-month period). Any additional requirements are specified within the module.

Safety laboratory assessments will be performed locally at each study site laboratory by means of their established methods. Therefore, the number of samples/blood volumes is subject to site-specific change.

Minor (non-substantial) changes in the timing or addition or deletion of time points for planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The IRB/independent ethics committee (IEC) will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

8.8.9 Storage, re-use and destruction of biomarker samples

The samples will be used up or disposed of after analyses or retained for further use as described here. Samples will be stored for a maximum of 15 years from the date of the Last Patient's Last Visit, after which they will be destroyed. The results of this biomarker research will be reported either in the CSR itself or as an addendum, or separately in a scientific report or publication. The results of this biomarker research may be pooled with biomarker data from other studies with the study drug to generate hypotheses to be tested in future research.

8.9 Medical Resource Utilisation and Health Economics

Medical Resource Utilisation and Health Economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

The statistical analyses will be performed by a contract research organisation (CRO) under the direction of the Early Clinical Biometrics Group, AstraZeneca.

A comprehensive SAP will be prepared. The primary aim of the study is to assess the efficacy, safety, and tolerability of multiple study drugs in patients with NSCLC, who progressed on an anti-PD-1/PD-L1 containing therapy.

9.1 Statistical hypotheses

Not applicable.

9.2 Sample size determination

Biomarker matched and non-matched cohorts (Group A and Group B)

The primary efficacy endpoint is ORR and this endpoint will be used to define the sample size. ORR is a well-established endpoint in early oncology studies, and in particular has been well reported in the literature for second-line NSCLC patients.

Per protocol version 9.0, there will be approximately 20 evaluable patients in each treatment cohort, with the option for possible expansion should an efficacy signal be observed, such as C observed confirmed responses (CR, PR). This may be to expand the size of a cohort C to include approximately CCI patients. Alternatively, patients could be enrolled to a non-comparative randomised expansion where approximately an additional C patients could be randomised to either study treatment or standard of care/treatment of physician's choice (to be determined and defined in the resulting protocol amendment).

An analysis will be carried out after approximately the CCI evaluable patient in a cohort, or the final patient dosed in a cohort if enrolment has ended early, has had the opportunity for 2 on-treatment RECIST assessments or has discontinued or withdrawn from treatment. The analysis will provide CCI and will also CCI in this cohort, should one exist.

If the true ORR is equal to CCI then there is a CCI out of C patients. Also, there is only a CCI to see CCI out of C if the true ORR is CCI

Confidence intervals (CIs) (Clopper-Pearson) will be constructed around the response rate observed in a cohort to enable decisions to be made around the likely success of future studies. For example, with 20 patients, if the following response rates were observed, the 80% CIs around those response rates would be:

- CCI the 2-sided 80% CIs would be CCI
- CCI the 2-sided 80% CIs would be CCI

In particular, there is 80% confidence that the true response rate would be between CCI if C responses out of C patients were observed.

With C patients, if the following response rates were observed the 80% CIs around those response rates would be:

- CCI the 2-sided 80% CIs would be CCI
- CCI the 2-sided 80% CIs would be CCI

Other efficacy endpoints including OS at 6, 9 and 12 months may be used to inform expansion decisions, but this has not formed part of the sample size calculations. Any decision to stop recruitment in a specific cohort will be at the discretion of AstraZeneca and will be based on emerging efficacy, safety, and tolerability data.

For Module 9, enrolment of an expanded cohort of approximately C evaluable patients was planned. This was based on encouraging preliminary data from Module 3. Data were to be reviewed after the first C patients in each treatment cohort and continue up to approximately C patients unless the emerging data review indicated a less than expected efficacy signal. Enrolment continued during the review of the data.

Following a regular data review (data cut-off 26 October 2021), the decision was made by AstraZeneca to close recruitment to Module 9 (both Cohorts CCI and to CCI

Per protocol version 10.0, the biomarker non-matched cohorts in Module 3 (B.3.ACQ and B.3.PRI) were each further expanded to include up to approximately C more patients (to a total of up to approximately C patients per non-matched cohort). Recruitment to Cohort A.3.ATM was also expanded to a total of approximately 40 patients. As per protocol version 12.0, all three cohorts in Module 3 have been close for enrolment.

Molecular aberration independent cohorts (Group C)

For Module 10, a total of up to approximately C patients, independent of their molecular aberration status, may be enrolled. Each cohort in Module 10 will explore a different dose of AZD6738 in combination with durvalumab: 160 mg BD and 240 mg BD (Cohort C.10.160 CCI respectively). Further details of the analyses to be performed for Module 10 are provided in Section 9.5.

For Module 11, a total of up to approximately C patients may be enrolled in a single cohort CCI to receive AZD6738 240 mg BD monotherapy. Further details of the analyses to be performed for Module 11 are provided in Section 9.5.

9.3 Populations for analyses

For purposes of analysis, the following populations are defined (Table 15).

Table 15 Study analysis populations

Population	Description
Screen Failure	All patients who sign the pre-screening ICF to participate in the study but do not meet the criteria for participation in the study, or are not subsequently assigned to a treatment cohort, or are assigned to a treatment cohort but not dosed.
Enrolled	All patients who sign the pre-screening ICF and have their treatment module allocation date recorded.
Safety	All enrolled patients who take ≥1 dose of the study drug. Patients will be analysed according to actual treatment received and corresponding assigned cohort.
Intention to treat (ITT)	All enrolled patients who take ≥1 dose of the study drug. Patients will be analysed according to their assigned cohort and planned treatment.
Evaluable for Response	Dosed patients who have measurable disease at baseline. Patients will be analysed according to their assigned cohort and planned treatment.
Evaluable for Confirmed Response	Dosed patients with measurable disease at baseline who have had the opportunity for ≥2 on-treatment RECIST scans (i.e., patients are dosed for at least 12 weeks) or who discontinue from the study or are withdrawn from study treatment at the time of data cut-off and are dosed for less than 12 weeks. This population will only be used for interim analyses. Patients will be analysed according to their assigned cohort and planned treatment.
Pharmacokinetics (PK)	All patients who provide concentration data for the study. Patients will be analysed according to the treatment they actually received.

Analysis sets will be defined as described above and subsets will be applied for the planned tables, figures and listings of study data according to whether they are related to the primary or re-allocated cohort. For re-allocated patients, analysis sets will be defined according to whether the patient received at least 1 dose of study drug after re-allocation to that module.
ICF informed consent form.

9.4 Statistical analyses

Analyses will be performed by AstraZeneca or its representatives. A comprehensive SAP will be developed and finalised before database lock and will describe the patient populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints. Any deviations from this plan will be reported in the clinical study report.

9.4.1 Definition of endpoints

Objective response rate

Objective response rate (ORR) is defined as the percentage of patients who have an objective response of confirmed CR or confirmed PR.

A confirmed response of CR/PR means that a response of CR/PR is recorded at 1 visit and confirmed by repeat imaging not less than 4 weeks after the visit when the response was first observed with no evidence of progression between the initial and CR/PR confirmation visit.

Data obtained up until progression, or last evaluable assessment in the absence of progression, will be included in the assessment of ORR. Patients who discontinue treatment without progression, receive a subsequent anti-cancer therapy and then respond will not be included as responders in the ORR.

Disease control rate

Disease control rate at 12 weeks

Disease control rate at 12 weeks is defined as the percentage of patients who have a best objective response (BoR) of CR or PR in the first 13 weeks (to allow for a late assessment within the assessment window) or who have SD for at least 11 weeks after start of treatment (to allow for an early assessment within the assessment window).

Disease control rate at 24 weeks

Disease control rate at 24 weeks is defined as the percentage of patients who have a BoR of CR or PR in the first 25 weeks (to allow for a late assessment within the assessment window) or who have SD for at least 23 weeks after start of treatment (to allow for an early assessment within the assessment window).

For cohorts with a Cycle 0, the SD requirement would be adjusted accordingly in line with the timing of the first scheduled RECIST assessment (further details are provided in the Statistical Analysis Plan).

Best percentage change from pre-dose in tumour size

The best percentage change from pre-dose in tumour size is the largest decrease (or smallest increase) for a patient using RECIST 1.1 assessments. All measurements up until disease progression or the last evaluable assessment to be included in the evaluation.

Duration of response

Duration of response will be defined as the time from the date of first documented response (which is subsequently confirmed) until date of documented progression or death in the absence of disease progression. The end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. The time of the initial response will be defined as the latest of the dates contributing towards the first visit response of PR or CR (which was subsequently confirmed). If a patient does not progress following a response, then their duration of response will use the PFS censoring time.

Progression free survival

Progression free survival is defined as the time from start of treatment until the date of objective disease progression according to RECIST 1.1 or death (by any cause in the absence of progression) regardless of whether the patient withdraws from therapy or receives another anti-cancer therapy prior to progression. Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST 1.1 assessment. However, if the patient progresses or dies after 2 or more missed visits, the patient will be censored at the time of the latest evaluable RECIST 1.1 assessment prior to the 2 missed visits. If the patient has no evaluable visits or does not have pre-dose data, they will be censored at Day 1 (date of first dose of study drug) unless they die within 2 visits of pre-dose.

The PFS time will always be derived based on scan/assessment dates, not visit dates.

RECIST assessments/scans contributing towards a particular visit may be performed on different dates. The following rules will be applied:

- Date of progression will be determined based on the earliest of the assessment/scan dates that led to assignment of PD by RECIST 1.1
- When censoring a patient for PFS the patient will be censored at the latest of the RECIST 1.1 assessment/scan dates contributing to a particular overall visit assessment

Overall visit assessments will be determined for each assessment (scheduled or unscheduled) and will contribute to the derivation of PFS.

Overall survival

Overall survival is defined as the time from the start of treatment until death due to any cause. Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive.

New lesions

A lesion identified at a follow-up assessment in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

Subsequent anti-cancer therapy

Subsequent anti-cancer therapy is expected to be initiated following cancer recurrence or development of a new cancer. Subsequent anti-cancer therapy relative to progression of the disease under investigation will be categorised as:

- Before progression (subsequent therapy is started prior to progression event during the study)

- No progression (subsequent therapy is started but the patient did not progress during the study)
- After progression.

Subsequent anti-cancer treatments include therapies with a start date after the last dose of any study treatment.

9.4.2 General considerations

Data will be presented by cohort within each module.

Biomarker matched and non-matched cohorts (Group A and Group B)

For each biomarker-matched cohort, the efficacy endpoints will be summarised for all patients and by their central test result. However, in certain circumstances (eg, if central test result not available) and as described in SAP, local biomarker test results may be used.

For each non-matched cohort, the efficacy endpoints will be summarised by the actual response (primary or acquired resistance) to prior PD-1/PD-L1 therapy.

An analysis will be performed after approximately the 20th evaluable patient in a cohort, or the final patient dosed in a cohort if enrolment has ended early, has had the opportunity for 2 on-treatment RECIST assessments or has discontinued or withdrawn from treatment. Each cohort will be analysed separately, unless stated otherwise. Details will be provided in the SAP. Due to the low prevalence of HER2 mutations, it is likely that fewer than 20 patients may be dosed in the A.6.HER2m cohort.

Molecular aberration independent cohorts (Group C)

For patients in Module 10 of Group C, data will be summarised by CCI and by CCI Data for all patients in Module 11 of Group C will be summarised together. Details of interim analyses are provided in Section 9.5.

Groups A, B and C

The analyses and summaries to be produced will be dependent on the number of patients recruited and will be detailed in the SAP.

Additional subgroup analyses may be performed and will be specified in the SAP.

Further survival data will continue to be collected until the planned database lock for a module, which can occur either 12 months after the last patient has started treatment or when 75% of the patients have died. Limited data for any patients who are ongoing on study

treatment in the module will be collected following the data cut-off for the module CSR (refer to the schedule of activities per module), and the survival follow-up will end for the module.

Final analysis of the last active cohort within the last module may be undertaken when the last patient has received 12 months of treatment, or all patients have discontinued or withdrawn from a module. Thereafter, patients who are still on study treatment can either choose to discontinue from the study or, where the investigator believes patients are gaining clinical benefit, patients may continue to receive study treatment following discussion with, and approval from, the sponsor. All patients will receive follow-up care in accordance with standard local clinical practice.

From protocol version 10.0 implementation, collection of follow-up survival data for screen failure patients is no longer required as sufficient data have now been collected to investigate the outcome in screen fail patients. Survival data collected for screen fail patients for visits prior to implementation of protocol version 10.0 will be summarised.

Re-allocated patients (applicable to Modules 1 to 5 in Groups A and B only) will be summarised for OS according to their original cohort. Their safety data in the new cohort will be listed only, except for death data for patients who die after they have been re-allocated, which will be included in the summary of deaths for the original cohort. Results from the exploratory biomarker research will be reported separately from the CSR for the main study.

Descriptive statistics will be used for all variables. Continuous variables will be summarised by the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarised by frequency counts and percentages for each category. Unless otherwise stated, percentages will be calculated out of the population total.

All data collected will be listed. Demographic data will be summarised on the intent-to-treat (ITT) analysis set. Exposure data will be summarised on the safety analysis set. The efficacy endpoints for tumour response (ORR, DCR and DoR) will be summarised on the evaluable for response analysis set. The efficacy endpoints for PFS and OS will be summarised on the ITT analysis set. Safety data will be summarised on the safety analysis set. Where applicable, PK data will be summarised on the PK analysis set.

9.4.3 Demographic data

Characteristics of the patients, including medical history and disease characteristics at pre-dose will be listed for each patient and summarised.

Reasons for discontinuation of study drug will be listed including the study day of treatment discontinuation and will be summarised.

9.4.4 Exposure

Exposure to study drug ie, total amount of study drug received will be listed for all patients. Total exposure will be summarised by the following: mean, standard deviation, minimum, maximum, median and number of observations. In addition, the number and percentage of patients with at least one dose interruption/dose delay and at least one dose reduction will be presented.

9.4.5 Efficacy analyses

9.4.5.1 Analysis of the primary variable

The ORR and its 80% CIs (Clopper-Pearson) will be summarised by cohort.

9.4.5.2 Analysis of the secondary variables

Disease control rate

Disease control rate and its 80% CIs (Clopper-Pearson) will be summarised by cohort.

Best percentage change from pre-dose in tumour size

Best percentage change from pre-dose in tumour size and its 80% CIs will be summarised. Waterfall plots indicating the best percentage change from pre-dose in sum of the diameters of TLs will be produced. Spider plots showing the percentage change from pre-dose in tumour size for each patient in a cohort with time will be produced.

Duration of response

If there are sufficient numbers of responders, and sufficient number of responses that have progressed by the point of the analysis, Kaplan-Meier plots of DoR in the responding patients will be produced and appropriate descriptive summary statistics will be presented (n, number of responders that have progressed or died, median and quartiles for DoR). Only patients who have a confirmed response will be included in this summary table.

Progression free survival

Summaries of PFS (n, events, medians, quartiles, proportion progression free at 3, 6, 9 and 12 months with 2-sided 80% CIs, and for the interim analysis only, corresponding 2-sided CCI CIs for CCI [redacted] will be provided, along with Kaplan-Meier plots.

Overall survival

Summaries of OS (n, deaths, medians, quartiles, proportion surviving at 3, 6, 9 and 12 months with 2-sided 80% CIs, and for the interim analysis only, corresponding 2-sided CCI [redacted] will be provided, along with Kaplan-Meier plots, as appropriate.

9.4.5.3 Analysis of exploratory variables

Assessment of survival in screen failure population

For all screen failure patients, OS (calculated from the date of consent to the date of death) will be summarised (n, deaths, medians, quartiles, proportion surviving at 3, 6, 9 and 12 months) by biomarker status where available, and Kaplan-Meier plots will be provided as appropriate. A summary of demographic characteristics will also be produced for the screen failure population.

9.4.6 Safety analyses

All patients who receive ≥1 dose of a study drug will be included in the assessment of the safety profile (safety analysis set). Appropriate summaries of all safety data will be produced, as defined below.

Data from all cycles of initial treatment will be combined in the presentation of safety data. Adverse events will be listed individually by patient. For patients who have a dose modification, all AEs (due to drug or otherwise) will be assigned to the initial dose.

The number of patients experiencing each AE will be summarised by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class, MedDRA preferred term and CTCAE grade (v4.03). The number and percentage of patients with AEs in different categories (eg, causally related, CTCAE Grade ≥3 etc) will be summarised by cohort, and events in each category will be further summarised by MedDRA system organ class and preferred term. SAEs will be summarised separately if a sufficient number occur.

Any AE occurring before the first dose of study drug (ie, before Cycle 0, Day 1, or Cycle 1, Day 1, as appropriate for each study cohort) will be included in the data listings but will not be included in the summary tables of AEs. Summary tables will include only treatment-emergent adverse events (TEAEs).

A TEAE is defined as follows:

- For patients not re-allocated to a second HUDSON treatment cohort:
  - TEAE is defined as an event with an onset date or worsening in CTCAE grade on or after the date of first dose of any study drug and up to and including 90 days following the date of last dose of study drug.
- For patients re-allocated to a second HUDSON treatment cohort:
  - TEAE is defined as any AE that started or worsened in CTCAE grade on or after the first dose of any study drug from the first cohort, until 90 days follow-up after discontinuation of study drug from the first cohort, unless the investigator assesses the relatedness of the AE with onset during this interval to the non-durvalumab study drug from the second cohort.

– For the re-allocated patients, only AEs occurring in the first cohort will be considered for summaries. AEs occurring in the second cohort will be flagged in the datasets and presented in the listings only.

Any AE occurring within the defined 90-day follow-up period after discontinuation of study drug, except for those with onset during this interval for which the investigator assesses the relatedness to the non-durvalumab study drug from the second cohort, will be included in the AE summaries. AEs occurring after the 90-day follow-up period after discontinuation of study drug, and AEs with onset during the defined 90-day follow-up period after discontinuation of study drug from the first cohort for which the investigator assesses the relatedness of the AE to the non-durvalumab study drug from the second cohort, will be listed separately, but not included in the summaries.

Haematology, clinical chemistry, coagulation, urinalysis, vital signs and ECG data will be listed individually by patient and suitably summarised. For all laboratory variables, which are included in the current version of CTCAE, the CTCAE grade will be calculated. Summary statistics of mean, median, standard deviation, minimum, maximum and number of observations will be used.

Details of any deaths will be listed for all patients.

Graphical presentations of safety data will be presented as is deemed appropriate.

9.4.7 Other analyses

9.4.7.1 Pharmacogenetics analyses

Blood samples will be collected and DNA will be derived from these blood samples, for future exploratory research into genes/genetic factors that may influence response eg, distribution, efficacy, safety, and tolerability of study treatments. Results of the exploratory pharmacogenetics research will not form part of the CSR.

9.4.7.2 Pharmacokinetics analyses

Plasma or serum concentrations of AZD9150 (Module 2), AZD6738 and durvalumab (Module 10), trastuzumab deruxtecan and durvalumab (Module 6), and cediranib (Module 7) will be measured. The data will be summarised and listed. The PK data may also be displayed graphically as appropriate. Samples below the lower limit of quantification will be treated as missing in the analyses. The PK data collected in this study may be utilised with data from other studies for population PK and/or PK/PD analyses.

9.4.7.3 Anti-drug antibodies against durvalumab, AZD9150, or trastuzumab deruxtecan

Immunogenicity results will be analysed descriptively by summarising the number and percentage of patients who develop detectable ADAs. The immunogenicity titre will be reported for samples confirmed positive for the presence of ADAs. The effect of immunogenicity on efficacy, safety and biomarker outcome will be evaluated, if the data allow.

9.5 Interim analyses

Biomarker matched and non-matched cohorts (Group A and Group B)

Analyses will be conducted in each cohort after approximately the CCI evaluable patient in a cohort, or the final patient dosed in a cohort if enrolment has ended early, has had the opportunity for 2 on-treatment RECIST assessments or has discontinued or withdrawn from treatment. This will coincide with planned analyses, approximately every CCI on efficacy and safety.

Molecular aberration independent cohorts (Group C)

Module 10

An CCI will be performed CCI following approximately CCI in the 160 mg cohort and approximately CCI in the 240 mg cohort first dose, or when approximately CCI in the 160 mg cohort and approximately CCI in the 240 mg cohort have discontinued or withdrawn from treatment. Based on observed efficacy, safety and tolerability data, each cohort may be increased to up to C patients. No statistical tests will be performed; all analyses will be descriptive. Further details will be provided in the SAP.

Module 11

A total of up to approximately C patients may be enrolled. A CCI will be carried out after approximately the CCI in the cohort has had the opportunity for 2 on-treatment RECIST assessments or has discontinued or withdrawn from treatment. If the CCI are not met CCI the cohort will be expanded and a second interim analysis will be carried out after the CCI evaluable patient in the cohort, or the final patient dosed in the cohort if enrolment has ended early, has had the opportunity for 2 on-treatment RECIST assessments, or has discontinued or withdrawn from treatment. There is the potential option to expand the cohort to C patients, should an efficacy signal, such as 4 or more confirmed responses out of the C patients, be observed, and supported by emerging data (including progressive disease rate, discontinuation rate and death rate). The CCI will provide CCI and will also CCI in this cohort, should one exist.

This decision framework is a recommendation only and any decision to stop or expand at any time will be at the discretion of the sponsor and will be based on emerging efficacy, safety and tolerability data.

9.5.1 Independent data monitoring committee (IDMC)

A data monitoring committee will be utilised for this study. Section A 5 provides more details on the rationale for and the remit of the committee.

The IDMC will review the safety data at approximately quarterly intervals and on-demand. Safety No-Go decision criteria, as described within the IDMC charter, have been developed using the methodology from Frewer et al 2016.

10. REFERENCES

Borghaei et al 2015
Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. N Engl J Med. 2015;373(17):1627-39.

Brahmer et al 2015
Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WE, Poddubskaya E, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N Engl J Med. 2015;373(2):123-35.

Carbone et al 2017
Carbone DP, Reck M, Paz-Ares L, Creelan B, Horn L, Steins M, et al; CheckMate 026 Investigators. First-Line Nivolumab in Stage IV or Recurrent Non-Small-Cell Lung Cancer. N Engl J Med. 2017;376(25):2415-2426.

Cockcroft and Gault 1976
Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31-41.

Eisenhauer et al 2009
Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer 2009;45:228–247.

Fossella et al 2004
Fossella FV, DeVore R, Kerr RN, Crawford J, Natale RR, Dunphy F, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. J Clin Oncol. 2000;18(12):2354-62. Erratum in: J Clin Oncol. 2004;22(1):209.

Frewer et al 2016
Frewer P, Mitchell P, Watkins C, Matcham J, et al. Decision-making in early clinical development. Pharm Stat. 2016 May; 15(3):255-63.

Gridelli et al 2015
Gridelli C, Rossi A, Carbone DP, Guarize J, Karachaliou N, Mok T, et al. Non-small-cell lung cancer. Nat Rev Dis Primers. 2015;1:15009.

Herbst et al 2016
Herbst RS, Baas P, Kim DW, Felip E, Pérez-Gracia JL, Han JY, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet. 2016;387(10027):1540-50.

Hirsch et al 2016
Hirsch FR, Suda K, Wiens J, Bunn PA Jr. New and emerging targeted treatments in advanced non-small-cell lung cancer. Lancet. 2016;388(10048):1012-24.

Langer et al 2016
Langer CJ, Gadgeel SM, Borghaei H, Papadimitrakopoulou VA, Patnaik A, Powell SF, et al. KEYNOTE-021 investigators. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. Lancet Oncol. 2016 Nov;17(11):1497-1508.

Lukas et al 2017
Lukas R, Gandhi M, O'Hear C, Hu S, Lai C, Patel J. Atezolizumab in Advanced NSCLC Patients with Baseline Brain Metastases: A Pooled Cohort Safety Analysis. J Thor Oncol. 2017 ;12(1) :S941-2.

Mazières et al 2013
Mazières J, Peters S, Lepage B, Cortot AB, Barlesi F, Beau-Faller M, et al. Lung cancer that harbors an HER2 mutation: epidemiologic characteristics and therapeutic perspectives. J Clin Oncol 2013;31(16):1997–2003.

NCCN 2017
NCCN® Clinical Practice Guidelines in Oncology for non-small cell lung cancer, version 8, 2017.

Oken et al 1982
Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP, et al. Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 1982:5;649-655.

Peters et al 2017
Peters S, Gettinger S, Johnson ML, Jänne PA, Garassino MC, Christoph D, et al. Phase II Trial of Atezolizumab As First-Line or Subsequent Therapy for Patients With Programmed Death-Ligand 1-Selected Advanced Non-Small-Cell Lung Cancer (BIRCH). J Clin Oncol. 2017;35(24):2781-2789.

Reck et al 2016
Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2016;375(19):1823-1833.

Rittmeyer et al 2017
Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, et al. OAK Study Group. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multi-centre randomised controlled trial. Lancet. 2017;389(10066):255-265.

Shaw et al 2014
Shaw AT, Ou SH, Bang YJ, Camidge DR, Solomon BJ, Salgia R, et al. Crizotinib in ROS1-rearranged non-small-cell lung cancer. N Engl J Med. 2014;371(21):1963–71.

Shepherd et al 2000
Shepherd FA, Dancey J, Ramlau R, Mattson K, Gralla R, O'Rourke M, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol. 2000;18(10):2095-103.

Topalian et al 2012
Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med. 2012;366(26):2443-54.

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, ethical and study oversight considerations

A 1 Regulatory and ethical considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.

AstraZeneca will be responsible for obtaining the required authorisations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO, but the accountability remains with AstraZeneca.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

The study will be performed in accordance with the AstraZeneca policy on Bioethics and Human Biological Samples.

Regulatory reporting requirements for SAEs

- Prompt notification by the investigator to AstraZeneca of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. AstraZeneca will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- For all studies except those utilising medical devices, investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- Adherence to European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from AstraZeneca will review and then file it along with the applicable IB and will notify the IRB/IEC, if appropriate according to local requirements.

Regulatory reporting requirements for serious breaches

- Prompt notification by the investigator to AstraZeneca of any (potential) serious breach of the protocol or regulations is essential so that legal and ethical obligations are met.
  - A ‘serious breach’ means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical study.
- If any (potential) serious breach occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives immediately after he or she becomes aware of it.
- In certain regions/countries, AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.
  - AstraZeneca will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority, IRB/IEC, and investigators. If EU Clinical Trials Regulation 536/2014 applies, AstraZeneca is required to enter details of serious breaches into the European Medicines Agency (EMA) Clinical Trial Information System (CTIS). It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.
- The investigator should have a process in place to ensure that:

- The site staff or service providers delegated by the investigator/institution are able to identify the occurrence of a (potential) serious breach.
- A (potential) serious breach is promptly reported to AstraZeneca or delegated party, through the contacts (email address or telephone number) provided by AstraZeneca.

A 2 Financial disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 3 Informed consent process

The investigator or his/her representative will explain the nature of the study to the patient or his/her legally authorised representative and answer all questions regarding the study.

Patients must be informed that their participation is voluntary. Patients or their legally authorised representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study site.

The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.

In recognition of the complexity of the HUDSON study, patients who are unable to sign the informed consent form themselves (loss of capacity) will not be approached for participation.

Patients must be reconsented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the patient or the patient's legally authorised representative.

If a patient declines to participate in any voluntary exploratory genetic research component of the study, there will be no penalty or loss of benefit to the patient and he/she will not be excluded from other aspects of the study.

If a patient's partner becomes pregnant during or within 6 months after the study, the partner is asked to sign the 'Adult Study Informed Consent Form for Pregnant Partners of Study Patients' and provide information about the pregnancy accordingly.

Patients who are re-screened are required to sign a new ICF.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorised designee will explain to each patient the objectives of the exploratory research. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. The patient will give a separate agreement to allow any remaining specimens to be used for exploratory research. Patients who decline to participate in this optional research will indicate this in the ICF. If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples already have been analysed at the time of the request, AstraZeneca will not be obliged to destroy the results of this research.

A 4 Data protection

Each patient will be assigned a unique identifier by the sponsor. Any patient records or data sets transferred to the sponsor will contain only the identifier; patient names or any information which would make the patient identifiable will not be transferred.

The patient must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

The patient must be informed that data will be collected only for the business needs. We will only collect and use the minimum amount of personal data to support our business activities and will not make personal data available to anyone (including internal staff) who is not authorised or does not have a business need to know the information.

The patient must be informed that in some cases their data may be pseudonymised. The General data Protection Regulation (GDPR) defines pseudonymisation as the processing of personal data in such a way that the personal data can no longer be attributed to a specific individual without the use of additional information, provided that such additional information is kept separately and protected by technical and organisational measures to ensure that the personal data are not attributed to an identified or identifiable natural person.

A 5 Committees structure

The safety of all AstraZeneca clinical studies is closely monitored on an on-going basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed; for instance, this could involve amendments to the CSP and letters to investigators.

An Independent Data Monitoring Committee (IDMC) is to be established to provide an independent, external, systematic, and unbiased assessment of safety for the HUDSON study. The role and the primary responsibilities of the IDMC members, as well as the purpose and timing of IDMC meetings are described in the IDMC charter. The IDMC will provide review independent of AstraZeneca, the HUDSON clinical team and all other individuals associated with the conduct of the HUDSON study.

A Steering Committee has been established to review relevant research (completed, ongoing, and pending) which may impact upon the study and to support the study team with interpretation of study outcomes. A Steering Committee Charter will define the primary responsibilities of the steering committee, its members, and the purpose and timing of meetings.

A Safety Review Committee (SRC) will be utilised, for those modules with a safety run-in, to review the emerging data. Members of the SRC will include relevant investigators and members of the AstraZeneca study team. The role, primary responsibilities of the SRC members, as well as the purpose and timing of SRC meetings are described in the SRC Charter.

A 6 Dissemination of clinical study data

Any results both technical and lay summaries for this trial, will be submitted to EU CTIS within a year from global End of Trial Date in all participating countries, due to scientific reasons, as otherwise statistical analysis is not relevant.

A description of this clinical study will be available on *http://astrazenecaclinicaltrials.com* and *http://www.clinicaltrials.gov,* as will the summary of the main study results when they are available. The clinical study and/or summary of main study results may also be available on other websites according to the regulations of the countries in which the study is conducted.

A 7 Data quality assurance

All patient data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are included in the Monitoring Plan.

AstraZeneca or designee is responsible for medical oversight throughout the conduct of the study which includes clinical reviews of study data in accordance with the currently approved protocol. Monitoring details describing clinical reviews of study data from a medical perspective are included in more detail in the Medical Monitoring Plan.

Study Monitors will perform ongoing source data verification as per the Monitoring Plan to confirm that data entered into the CRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 25 years after study archiving, unless otherwise specified by local regulations, according to the AstraZeneca Global retention and Disposal (GRAD) Schedule. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

A 8 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator’s site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Source data may include, but is not limited to: medical history and physical examination notes, hospital discharge summary, autopsy report when available, results of relevant diagnostic tests completed.

A 9 Publication policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multi-centre studies only in their entirety and not as individual site data. In this case, a co-ordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

A 10 Site closure

The sponsor designee reserves the right to close the study site or terminate the study at any time and for any reason at the sole discretion of the sponsor. The study may be stopped if, in the judgment of AstraZeneca, trial subjects are placed at undue risk because of clinically significant findings that:

- meet individual stopping criteria or are otherwise considered significant
- are assessed as causally related to study drug,
- are not considered to be consistent with continuation of the study.

Regardless of the reason for termination, all data available for the subject at the time of discontinuation of follow-up must be recorded in the CRF. All reasons for discontinuation of treatment must be documented.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the subjects' interests.

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development.

Appendix B Adverse event definitions and additional safety information

B 1 Definition of adverse events

An AE is the development of any untoward medical occurrence in a patient or clinical study patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study treatment has been administered.

B 2 Definitions of serious adverse event

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the patient or may require medical treatment to prevent one of the outcomes listed above.

B 3 Life-threatening

'Life-threatening' means that the patient was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the patient's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

B 4 Hospitalisation

Outpatient treatment in an emergency room is not in itself a SAE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

B 5 Important medical event or medical treatment

Medical and scientific judgment should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardise the patient or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgment must be used.

- Angioedema not severe enough to require intubation but requiring IV hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

B 6 Intensity rating scale

The grading scales found in the revised National Cancer Institute CTCAE version 4.03 will be utilised for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate and severe events into CTCAE grades should be used. A copy of the CTCAE can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

It is important to distinguish between SAEs and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Appendix B 2.

B 7 A guide to interpreting the causality question

When making an assessment of causality consider the following factors when deciding if there is a ‘reasonable possibility’ that an AE may have been caused by the drug.

- Time course. Exposure to suspect drug. Has the patient actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

B 8 Medication error, drug abuse, and drug misuse

Medication error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study drug that either causes harm to the patient or has the potential to cause harm to the patient.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or patient.

Medication error includes situations where an error:

- occurred
- was identified and intercepted before the patient received the drug
- did not occur, but circumstances were recognised that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the patient
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed eg, kept in the fridge when it should be at room temperature
- Wrong patient received the medication (excluding interactive voice response system [IVRS]/ interactive web response system [IWRS] errors)
- Wrong drug administered to patient (excluding IVRS/IWRS errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IVRS/IWRS - including those which lead to one of the above listed events that would otherwise have been a medication error
- Patient accidentally missed drug dose(s) eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Patient failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open-label studies, even if an AstraZeneca product

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

Drug abuse

For the purpose of this study, drug abuse is defined as the persistent or sporadic intentional, non-therapeutic excessive use of an AstraZeneca study drug for a perceived reward or desired non-therapeutic effect.

Any events of drug abuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Abuse Report Form. This form should be used both if the drug

abuse happened in a study patient or if the drug abuse involves a person not enrolled in the study (such as a relative of the study patient).

Examples of drug abuse include but are not limited to:

- The drug is used with the intent of getting a perceived reward (by the study patient or a person not enrolled in the study)
- The drug in the form of a tablet is crushed and injected or snorted with the intent of getting high

Drug misuse

Drug misuse is the intentional and inappropriate use (by a study patient) of an AstraZeneca study drug for medicinal purposes outside of the authorised product information, or for unauthorised AstraZeneca study drugs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

Events of drug misuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Misuse Report Form. This form should be used both if the drug misuse happened in a study patient or if the drug misuse regards a person not enrolled in the study (such as a relative of the study patient).

Examples of drug misuse include but are not limited to:

- The drug is used with the intention to cause an effect in another person
- The drug is sold to other people for recreational purposes
- The drug is used to facilitate assault in another person
- The drug is deliberately administered by the wrong route
- The drug is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole
- Only half the dose is taken because the study patient feels that he/she is feeling better when not taking the whole dose
- Someone who is not enrolled in the study intentionally takes the drug

Appendix C Handling of Human Biological Samples

C 1 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The investigator at each centre keeps full traceability of collected biological samples from the patients while in storage at the centre until shipment or disposal (where appropriate).

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

AstraZeneca will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers

Samples retained for further use will be stored in the AZ-assigned biobanks and will be registered by the AstraZeneca Biobank Team during the entire life cycle.

C 2 Withdrawal of Informed Consent for donated biological samples

If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

The investigator:

- Ensures patients' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca and documented on the withdrawal of consent checklist
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the organisation(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the signed document returned to the study site
- Ensures that the patient and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organisation(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

C 3 International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories (http://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx). For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and Categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg, Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, hepatitis A, B, C, D, and E viruses, HIV types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (https://www.iata.org/whatwedo/cargo/dgr/Documents/DGR-60-EN-PI650.pdf)
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable
- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging/containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Appendix D Genetics

D 1 Use/analysis of DNA

Genetic variation may impact a patient's response to therapy, susceptibility to, and severity and PD. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease aetiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting patients.

AstraZeneca intends to collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. Genetic research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in health care and to the discovery of new diagnostics, treatments or medications.

In addition, collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials and, possibly, to genetically guided treatment strategies.

Genetic research may consist of the analysis of the structure of the patient´s DNA, ie, the entire genome.

The results of genetic analysis that form part of the optional genomic sample will be communicated via publication in peer-reviewed journals upon completion of analysis. There are currently no plans to analyse and report data from each module in isolation. The results of the genetic analysis will be reported as appropriate in peer-reviewed journals. The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

The samples will be retained while research on the study drugs in this protocol continue but no longer than 15 years or other period as per local requirements.

D 2 Genetic research plan and procedures

Selection of genetic research population

Study selection record

All patients will be asked to participate in this genetic research. Participation is voluntary and if a patient declines to participate there will be no penalty or loss of benefit. The patient will not be excluded from any aspect of the main study.

Inclusion criteria

- For inclusion in this genetic research, patients must fulfil all of the inclusion criteria described in the main body of the CSP **and** provide informed consent for the genetic sampling and analyses.

Exclusion criteria

Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:

- Previous allogeneic bone marrow transplant
- Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection

Withdrawal of consent for genetic research

Patients may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary discontinuation will not prejudice further treatment. Procedures for discontinuation are outlined in Section 7 of the core CSP.

Collection of samples for genetic research

The blood sample for genetic research will be obtained from the patients at screening. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an AE, such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn at screening, it may be taken at any visit until the last study visit. Only one sample should be collected per patient for genetics during the study. Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

Coding and storage of DNA samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. Samples will be stored for a maximum of 15 years, from the date of last patient last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

An additional second code will be assigned to the blood either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable only by the second, unique number. This number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated organisation. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organisations working with the DNA).

The link between the patient enrolment code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organisations. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and permit tracing of samples for destruction in the case of withdrawal of consent.

Ethical and regulatory requirements

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Appendix A.

Informed consent

The genetic component of this study is optional and the patient may participate in other components of the main study without participating in the genetic component. To participate in the genetic component of the study the patient must sign and date both the consent form for the main study and the genetic component of the study. Copies of both signed and dated consent forms must be given to the patient and the original filed at the study site. The Principal Investigator(s) is responsible for ensuring that consent is given freely and that the patient understands that they may freely discontinue from the genetic aspect of the study at any time.

Patient data protection

AstraZeneca will not provide individual genotype results to patients, any insurance company, any employer, their family members, general physician unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a patient's identity and also have access to his/her genetic data. Also, Regulatory authorities may require access to the relevant files, though the patient's medical information and the genetic files would remain physically separate.

Data management

Any genotype data generated in this study will be stored at a secure system at AstraZeneca and/or designated organisations to analyse the samples.

AstraZeneca and its designated organisations may share summary results (such as genetic differences from groups of individuals with a disease) from this genetic research with other researchers, such as hospitals, academic organisations or health insurance companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can

only use this information for health-related research purposes. Researchers may see summary results but they will not be able to see individual patient data or any personal identifiers.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

Statistical methods and determination of sample size

The number of patients that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a statistical evaluation or whether only descriptive statistics will be generated. A Statistical Analysis Plan (SAP) may be prepared where appropriate.

Appendix E Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law

E 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report cases of Potential Hy's Law (PHL) and Hy's Law (HL). It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a patient meets PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory **and/or** elevated TBL from a local laboratory.

The investigator will also review Adverse Event data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than drug induced liver injury (DILI) caused by the study drug.

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Serious Adverse Events (SAEs) and Adverse Events (AEs) according to the outcome of the review and assessment in line with standard safety reporting processes.

E 2 Definitions

Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥3x Upper Limit of Normal (ULN) **together with** Total Bilirubin (TBL) ≥2xULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

Hy's Law (HL)

AST or ALT ≥3xULN **together with** TBL ≥2xULN, where no other reason, other than the study drug, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified time frame within which the elevations in transaminases and TBL must occur.

E 3 Identification of potential Hy's Law cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any subject who meets any of the following identification criteria in isolation or in combination:

- ALT ≥3xULN
- AST ≥3xULN
- TBL ≥2xULN

Local laboratories being used:

The investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Determine whether the subject meets PHL criteria (see Section E2 within this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

E 4 Follow-up

E 4.1 Potential Hy's Law criteria not met

If the subject does not meet PHL criteria the investigator will:

- Perform follow-up on subsequent laboratory results according to the guidance provided in the clinical study protocol

E 4.2 Potential Hy's Law criteria met

If the subject does meet PHL criteria the investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team
- Within 1 day of PHL criteria being met, the investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting.
- For subjects that met PHL criteria prior to starting study drug, the investigator is not required to submit a PHL SAE unless there is a significant change in the subject's condition

- The Study Physician contacts the investigator, to provide guidance, discuss and agree an approach for the study subjects' follow-up (including any further laboratory testing) and the continuous review of data
  - Subsequent to this contact the investigator will:
    - Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Complete follow-up SAE Form as required.
    - Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Study Physician
    - Complete the three Liver CRF Modules as information becomes available

E 5 Review and assessment of potential Hy's Law cases

The instructions in this section should be followed for all cases where PHL criteria are met.

As soon as possible after the biochemistry abnormality was initially detected, the Study Physician contacts the investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the study drug, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the investigator will follow the instructions below.

Where there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF
- If the alternative explanation is an AE/SAE: update the previously submitted Potential Hy's Law SAE and AE CRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AstraZeneca standard processes

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the study drug:

- Send updated SAE (report term 'Hy's Law') according to AstraZeneca standard processes.

- The 'Medically Important' serious criterion should be used if no other serious criteria apply
- As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If there is an unavoidable delay of over 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provides any further update to the previously submitted SAE of Potential Hy's Law, (report term now 'Hy's Law case') ensuring causality assessment is related to study drug and seriousness criteria is medically important, according to CSP process for SAE reporting
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

E 6 Actions required for repeat episodes of potential Hy's Law

This section is applicable when a patient meets PHL criteria on study treatment, and has already met PHL criteria at a previous on study treatment visit.

The requirement to conduct follow-up, review, and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

> Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study eg, chronic or progressing malignant disease, severe infection or liver disease.

If **No**: Follow the process described in Appendix E4.2 for reporting PHL as an SAE.

If **Yes**: Determine if there has been a significant change in the subject's condition[#] compared with when PHL criteria were previously met.

- If there is no significant change, no action is required.
- If there is a significant change, follow the process described in Appendix E4.2 for reporting PHL as an SAE.

[#]A 'significant' change in the subject's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator; this may be in consultation with the study physician if there is any uncertainty.

E 7 Laboratory tests

The list below represents the standard, comprehensive list of follow-up tests which are recommended but not mandatory when using a central laboratory. For studies using a local laboratory, the list may be modified based on clinical judgement. If required, additional assistance on which tests could be used to evaluate other potential causes of liver dysfunction consult with the Hepatic Safety Knowledge Group. Any test results need to be recorded.

Hy's Law lab kit for central laboratories (18 December 2018)

Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR
Viral hepatitis	IgM anti-HAV IgM and IgG anti-HBc HBsAg HBV DNA IgG anti-HCV HCV RNA* IgM anti-HEV HEV RNA
Other viral infections	IgM & IgG anti-CMV IgM & IgG anti-HSV IgM & IgG anti-EBV
Alcoholic hepatitis	Carbohydrate deficient transferrin (CD-transferrin)**
Autoimmune hepatitis	Antinuclear antibody (ANA) Anti-Liver/Kidney Microsomal Ab (Anti-LKM) Anti-Smooth Muscle Ab (ASMA)
Metabolic diseases	alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin Transferrin saturation

* HCV RNA is only tested when IgG anti-HCV is positive or inconclusive
** Carbohydrate deficient transferrin (CD-transferrin) is not available in China. Study teams should amend this list accordingly

REFERENCES

Aithal et al 2011, Clinical Pharmacology and Therapeutics 89(6):806-815.

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation'

Appendix F Abbreviations

Abbreviation or special term	Explanation
5-HT3	5-hydroxytryptamine
ADA	Anti-drug antibodies
AE	Adverse event
AESI	Adverse event of special interest
ALK	Anaplastic lymphoma kinase
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AML	Acute myeloid leukaemia
AMP	Adenosine monophosphate
ANC	Absolute neutrophil count
APC	Antigen presenting cell
APTT	Activated partial thromboplastin time
ASO	Antisense oligonucleotide
AST	Aspartate aminotransferase
ATM	Ataxia telangiectasia mutated
ATR	Ataxia telangiectasia and Rad3-related protein
AUC	Area under the curve
AUC_{ss}	Area under the plasma concentration-time curve at steady state
AZ DES	AstraZeneca Patient Safety data entry site
BCRP	Breast cancer resistance protein
bd	Twice daily
BICR	Blinded independent central review
BoR	Best objective response
BP	Blood pressure
BRCA	Breast cancer associated gene
BUN	Blood urea nitrogen
CAP	College of American Pathologists
CART	Cell-free and concentrated ascites reinfusion therapy
CCTG	Canadian Clinical Trials Group
CD	Cluster of differentiation
CHF	Congestive heart failure
CI	Confidence interval
c-kit	Stem cell factor receptor

Abbreviation or special term	Explanation
CL/F	Apparent total clearance of the drug from plasma after oral administration
CLIA	Clinical Laboratory Improvement Amendments
CLL	Chronic lymphocytic leukaemia
C_{max}	Maximum plasma concentration
$C_{max,ss}$	Maximum plasma concentration at steady state
C_{min}	Minimum plasma concentration
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus Disease 2019
CR	Complete response
CrCl	Creatinine clearance
CRO	Contract research organisation
CRP	C-reactive protein
CSP	Clinical study protocol
CSR	Clinical study report
$C_{ss,min}$	Minimum plasma concentration at steady state
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CCI	[redacted]
CTLA4	Cytotoxic T-lymphocyte associated protein 4
$C_{trough,ss}$	Trough plasma concentration at steady state
CXCL	C-X-C motif ligand
CYP3A	Cytochrome P450 3A
CYP3A4	Cytochrome P450 3A4
DAR	Drug-antibody ratio
DBP	Diastolic blood pressure
DCR	Disease control rate
DES	Data entry site
DILI	Drug induced liver injury
DLBCL	Diffuse large B-cell lymphoma
DLCO	Diffusion lung carbon monoxide
DLT	Dose-limiting toxicity
DoR	Duration of response
DSB	Double strand DNA break
ECG	Electrocardiogram
ECHO	Echocardiogram

Abbreviation or special term	Explanation
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EGFR	Epidermal growth factor receptor
EGFRm NSCLC	Epidermal growth factor receptor mutant non-small cell lung cancer
EMA	European Medicines Agency
ESR	Externally Sponsored Research
EU	European Union
FDA	Food and Drug Administration
FDG-PET	18F-Fluoro-deoxyglucose positron emission tomography
Fe%	Percentage of dose eliminated
FFPE	Formalin-fixed paraffin-embedded
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GI	Gastrointestinal
G_{LSmean}	Geometric least squares mean
GMP	Good Manufacturing Practice
Hb	Haemoglobin
HBc	Hepatitis B core
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
hCG	Human chorionic gonadotrophin
HCV	Hepatitis C virus
HDV	Hepatitis D virus
HER2	Human epidermal growth factor receptor 2
HIV	Human immunodeficiency virus
HL	Hy's Law
HLA	Human leukocyte antigen
HNSCC	Head and neck squamous cell carcinoma
HRCT	High resolution computed tomography
HRR	Homologous recombination repair gene
HRRm	Mutation detected in a homologous recombination repair gene
IATA	International Airline Transportation Association
IB	Investigator's Brochure

Abbreviation or special term	Explanation
IBW	Ideal body weight
IC	Immune cell
IC_{50}	Concentration of an inhibitor where binding is reduced by 50%
IC_{90}	Concentration of an inhibitor where binding is reduced by 90%
ICF	Informed consent form
ICH	International Council for Harmonisation
ICR	Independent central review
IDMC	Independent Data Monitoring Committee
IEC	Independent ethics committee
IFN	Interferon
Ig	Immunoglobulin
IHC	Immunohistochemistry
ILD	Interstitial lung disease
imAE	Immune-mediated adverse event
INR	International normalised ratio
International Co-ordinating investigator	If a study is conducted in several countries the international co-ordinating investigator is the investigator co-ordinating the investigators and/or activities internationally.
irAE	Immune-related adverse event
IRB	Institutional review board
IRF	Interferon regulatory factor
IRT	Interactive response technology
ITT	Intention to treat
IUD	Intrauterine device
IV	Intravenous
IVRS	Interactive voice response system
IWRS	Interactive web response system
LKB1	Liver kinase B1
LLN	Lower limit of normal
LVEF	Left ventricular ejection fraction
mAb	Monoclonal antibody
MAP	Managed Access Programme
MATE	Multidrug and toxin extrusion protein
mCRPC	Metastatic castration-resistant prostate cancer
MDR1	Multidrug resistance protein 1

Abbreviation or special term	Explanation
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MRI	Magnetic resonance imaging
mRNA	Messenger RNA
MTD	Maximum tolerated dose
mTOR	Mammalian target of rapamycin
MUGA	Multigated acquisition scan
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	Not evaluable
NFκB	Nuclear factor kappa B
NGS	Next generation sequencing
NK	Neurokinin
NK1	Neurokinin 1 receptor
NSCLC	Non-small cell lung cancer
NTL	Non-target lesion
OATP	Organic anion-transporting protein
OCT	Organic cation transporter
od	Once daily
ORR	Objective response rate
OS	Overall survival
Panc	Pancreatic adenocarcinoma
PARP	Polyadenosine 5'diphosphoribose (poly [ADP ribose]) polymerisation
PBMC	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
PD	Progression of disease
PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
PDGFR	platelet-derived growth factor receptor
PFS	Progression free survival
P-gp	P-glycoprotein
PHL	Potential Hy's Law
PI3K	Phosphatidylinositol-3 kinase related kinases (PIKKs).
PIKK	Phosphatidylinositol-3 kinase related kinase

Abbreviation or special term	Explanation
PK	Pharmacokinetic(s)
PK/PD	Pharmacokinetic/pharmacodynamic
PP	Per protocol
PR	Partial response
pRAD50	Phosphorylated RAD50
PRES	Posterior reversible encephalopathy syndrome
PFR	Patient registration form
Q2W	Every 2 weeks
Q3W	Every 3 weeks
Q4W	Every 4 weeks
Q12W	Every 12 weeks
Q24W	Every 24 weeks
QTc	Corrected QT interval
QTcF	QT interval corrected for heart rate using Fridericia's correction factor
QW	Every week
RANKL	Receptor activator of nuclear factor kappa-B ligand
RECIST 1.1	Response Evaluation Criteria in Solid Tumours, version 1.1
CCI	[redacted]
RM-SCCHN	Recurrent/metastatic squamous cell carcinoma of the head and neck
ROS1	c-ros oncogene 1
RP2D	Recommended Phase 2 dose
RT	Radiation therapy
RT PCR	Reverse transcription polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SBP	Systolic blood pressure
SCCHN	Squamous cell carcinoma of the head and neck
SCLC	Small cell lung cancer
SD	Stable disease
SoA	Schedule of Activities
sPD-L1	Soluble programmed cell death ligand 1
SpO_2	Saturation of peripheral oxygen
SRC	Safety Review Committee

Abbreviation or special term	Explanation
SSB	Single strand DNA break
STAT3	Signal transducer and activator of transcription 3
STING	Stimulator of interferon genes
STK11	Serine threonine kinase 11
SUSAR	Suspected unexpected serious adverse reaction
T_3	Triiodothyronine
T_4	Thyroxine
TBK	Tank binding kinase
TBL	Total bilirubin
TC	Tumour cell
TCR	T cell receptor
T-DM1	Trastuzumab emtansine
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TKI	Tyrosine kinase inhibitor
TL	Target lesion
T_{max}	Time to reach maximum plasma concentration following drug administration
TOR	Target of rapamycin
TORC	Target of rapamycin complex
TSH	Thyroid-stimulating hormone
UC	Urothelial carcinoma
ULN	Upper limit of normal
UPC	Urine protein:creatinine ratio
US	United States
VEGF	Vascular endothelial growth factor
WHO	World Health Organization
w/v	Weight/volume

Appendix G Guidelines for evaluation of objective tumour response using RECIST 1.1 criteria (Response Evaluation Criteria in Solid Tumours)

G 1 Introduction

This appendix details the implementation of RECIST 1.1 guidelines (Eisenhauer et al 2009) for the D6185C00001 study with regards to investigator assessment of tumour burden including protocol-specific requirements for this study.

G 2 Definition of measurable, non-measurable, target, and non-target lesions

Only patients with measurable disease at pre-dose should be included in the study. Measurable disease is defined by the presence of at least one measurable lesion which has not been previously irradiated.

Tumour lesions selected for screening biopsy must not be used as index lesions, unless there are no other lesions suitable for biopsy.

Measurable

A lesion, not previously biopsied per the protocol prior to treatment allocation, that can be accurately measured at pre-dose as ≥10 mm in the longest diameter (except lymph nodes which must have short axis[1] ≥15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) and which is suitable for accurate repeated measurements.

Non-measurable

- All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 mm to <15 mm short axis at pre-dose[2]).
- Truly non-measurable lesions include the following: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by CT or MRI.
- Tumour lesions selected for screening biopsy
- Previously irradiated lesions, unless lesion has clearly progressed
- Skin lesions assessed by clinical examination
- Brain metastasis

[1] Lymph node short axis = longest axis perpendicular to long axis

[2] Nodes with <10 mm short axis are considered non-pathological and should not be recorded or followed as non-target lesions (NTLs).

Special cases

- Lytic bone lesions or mixed lytic–blastic lesions, with identifiable soft tissue components, can be considered measurable if the soft tissue component meets the definition of measurability. Blastic lesions are considered non-measurable.
- Cystic metastases can be considered measurable lesions if they meet the criteria for measurability from a radiological point of view, but if non-cystic lesions are present in the same patient, these should be selected as TLs.

Target lesions:

A maximum of 5 measurable lesions (with a maximum of 2 lesions per organ), representative of all lesions involved suitable for accurate repeated measurement, should be identified as TLs at pre-dose.

Non-target lesions:

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at pre-dose.

G 3 Methods of assessment

The same method of assessment on the same imaging technique should be used to characterise each identified and recorded lesion at pre-dose and during follow-up visits.

A summary of the methods to be used for RECIST assessment is provided in Table G1, and those excluded from tumour assessments for this study are highlighted with the rationale provided.

Table G1 Summary of methods of assessment

Target lesions	Non-target lesions	New lesions
CT (preferred)	CT (preferred)	CT (preferred)
MRI	MRI	MRI
	Clinical examination	Clinical examination
	X-ray, Chest X-ray	X-ray, Chest X-ray
		Ultrasound
		Bone scan
		FDG-PET

CT Computed tomography; FDG-PET 18F-Fluoro-deoxyglucose positron emission tomography; MRI Magnetic resonance imaging.

G 3.1 CT and MRI

Computed tomography and MRI, each preferably with IV contrast, are generally considered to generate the best currently available and reproducible images for measurement of TL, assessment of NTL, and identification of any new lesions.

In the D6185C00001 (HUDSON) study it is recommended that CT examinations of the chest, abdomen (including liver and adrenal glands), and pelvis will be used to assess tumour burden at pre-dose and follow-up visits. CT examination with IV contrast media administration is the preferred method. Magnetic resonance imaging should be used where CT is not feasible or it is medically contraindicated. These modalities can be combined; eg, in patients who are sensitive to IV CT contrast, a non-contrast CT exam of the chest and an MRI with IV contrast of the abdomen would be the appropriate combination. For brain lesion assessment, MRI with IV contrast is the preferred method.

G 3.2 Clinical examination

Clinical examination will not be used for assessment of TL. Clinically detected lesions can be selected as TLs if they are assessed by CT or MRI scans. Clinical examination can be used to assess NTL and to identify the presence of new lesions.

G 3.3 X-ray

G 3.3.1 Chest X-ray

Chest X-ray assessment will not be used for assessment of TL as they will be assessed by CT examination or MRI examination. Chest X-ray can, however, be used to assess NTL and to identify the presence of new lesions.

G 3.3.2 Plain X-ray

Plain X-ray may be used as a method of assessment for bone NTL and to identify the presence of new bone lesions.

G 3.4 Ultrasound

Ultrasound examination will not be used for assessment of TL and NTL as it is not a reproducible method, does not provide an accurate assessment of tumour size, and it is subjective and operator dependent. Ultrasound examination can, however, be used to identify the presence of new lesions. If new clinical symptoms occur and an ultrasound is performed then new lesions should be confirmed by CT or MRI examination.

G 3.5 Endoscopy and laparoscopy

Endoscopy and laparoscopy will not be used for tumour assessments as they are not validated in the context of tumour assessment.

G 3.6 Tumour markers

Tumour markers will not be used for tumour response assessments as per RECIST 1.1.

G 3.7 Cytology and histology

Histology will not be used as part of the tumour response assessment as per RECIST 1.1. Cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment is required when the measurable tumour has met criteria for response or stable disease. In such circumstances, the cytology is necessary to differentiate between response/stable disease (an effusion may be a side effect of the treatment) and PD (if the neoplastic origin of the fluid is confirmed). Where cytology findings are not available, any effusion that significantly worsens (from trace to large) or appearance of clinically significant effusion (requiring change in drug therapy) during the study treatment will be considered to be progression of NTL, or disease progression due to new lesions.

G 3.8 Isotopic bone scan

Bone lesions identified on an isotopic bone scan at pre-dose and confirmed by CT, MRI, or X-ray at pre-dose should be recorded as NTL and followed by the same method as per pre-dose assessment.

Isotopic bone scans may be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. New lesions will be recorded where a positive hot-spot that was not present on the pre-dose bone scan assessment is identified on a bone scan performed at any time during the study. The investigator should consider the positive hot-spot to be a significant new site of malignant disease and represent true disease progression in order to record the new lesion. Confirmation by CT, MRI and X-ray is recommended where bone scan findings are equivocal.

G 3.9 FDG-PET scan

18F-Fluoro-deoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) scans may be used as a method for identifying new lesions, according with the following algorithm: New lesions will be recorded where there is positive 18F-Fluoro-deoxyglucose uptake not present on pre-dose FDG-PET scan or in a location corresponding to a new lesion on CT/MRI at the same follow-up visit. If there is no pre-dose FDG-PET scan available, and no evidence of new lesions on CT/MRI scans then follow-up CT/MRI assessments should be continued, scheduled as per protocol or clinical indicated, in order to confirm new lesions.

G 4 Tumour response evaluation

G 4.1 Schedule of evaluation

The methods of assessment of tumour burden used at pre-dose CT/MRI scans of the chest, abdomen (including liver and adrenal glands), and pelvis must be used at each subsequent follow-up assessment. Additional imaging may be performed based on the signs and symptoms of the patient, eg, new lesions at follow-up.

Pre-dose assessments should be performed no more than 28 days before start of study treatment (see Table 1 in the core protocol), and ideally should be performed as close as possible to the start of study drug.

Tumour assessments should be performed every 6 weeks (±1 week) for the first 24 weeks relative to the start of combination therapy (Cycle 1, Day 1), and every 8 weeks (±1 week) (unless otherwise specified in the SoA of the module). (Note: More frequent scanning is permitted where this is the local standard), until objective disease progression as defined by RECIST 1.1, and confirmed with a subsequent scan (no earlier than 4 weeks after initial progressive disease assessment) in the absence of clinically significant deterioration as determined by the investigator.

Disease progression requires confirmation; the confirmatory scan should occur no earlier than 4 weeks after the prior assessment of PD in the absence of clinically significant deterioration. If progression is not confirmed, then the patient should continue on study treatment and on treatment assessments.

If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits. This schedule is to be followed in order to minimise any unintentional bias caused by some patients being assessed at a different frequency than other patients.

Additional assessments will be performed post confirmed objective disease progression for patients remaining on study drug treatment, re-treatment, or until subsequent cancer therapy according to the CSP. In addition, patients will continue receiving scheduled radiological scans, per protocol, for as long as they are undergoing study treatment (see Section 1.1, Schedule of Activities, for each module). Following the data cut-off for the respective module CSR, the frequency of scans should be as per standard of care.

G 4.2 Target lesions

G 4.2.1 Documentation of target lesions

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes as a single organ), representative of all lesions involved should be identified as

TL at pre-dose. Target lesions should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis for nodal lesions), but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

The site and location of each TL should be documented as well as the longest diameter for non-nodal lesions (or short axis for lymph nodes). All measurements should be recorded in millimetres. At pre-dose the sum of the diameters for all TL will be calculated and reported as the pre-dose sum of diameters. At follow-up visits the sum of diameters for all TL will be calculated and reported as the follow-up sum of diameters.

Special cases:

For TL measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis.

If the CT/MRI slice thickness used is >5 mm, the minimum size of measurable disease at pre-dose should be twice the slice thickness of the pre-dose scan.

If a lesion has completely disappeared, the longest diameter should be recorded as 0 mm.

If a TL splits into two or more parts, then record the sum of the diameters of those parts.

If two or more TLs merge then the sum of the diameters of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion(s).

If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5 mm.

If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion.

When a TL has had any intervention eg, definitive radiotherapy, embolization, surgery, etc. during the study, the size of the TL should still be provided where possible.

G 4.2.2 Evaluation of target lesions

This section provides the definitions of the criteria used to determine objective tumour visit response for TL (see Table G2).

Table G2 Evaluation of target lesions

Complete Response (CR)	Disappearance of all TLs since pre-dose. Any pathological lymph nodes selected as TLs must have a reduction in short axis to < 10 mm
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of TL, taking as reference the pre-dose sum of diameters
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD
Progression of disease (PD)	At least a 20% increase in the sum of diameters of TLs, taking as reference the smallest sum on study (this includes the pre-dose sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of ≥ 5 mm.
Not Evaluable (NE)	Only relevant if any of the TLs at follow-up were not assessed or not evaluable (eg, missing anatomy) or had a lesion intervention at this visit. Note: If the sum of diameters meets the PD criteria, PD overrides not evaluable as a TL response

PD progression of disease; TL target lesion

G 4.3 Non-target lesions

G 4.3.1 Evaluation of non-target lesions

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at pre-dose. Measurements are not required for these lesions, but their status should be followed at subsequent visits. At each visit an overall assessment of the NTL response should be recorded by the investigator. This section provides the definitions of the criteria used to determine and record overall response for NTL at the investigational site at each visit (see Table G3).

Table G3 Evaluation of non-target lesions

Complete Response (CR)	Disappearance of all NTLs since pre-dose. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non CR/Non PD	Persistence of one or more NTL.
Progression (PD)	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
Not Evaluable (NE)	Only relevant when one or some of the NTLs were not assessed and, in the investigator's opinion, they are not able to provide an evaluable overall NTL assessment at this visit. Note: For patients without TLs at pre-dose, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met.

NTL, non-target lesion; TL, target lesion

To achieve 'unequivocal progression' on the basis of NTLs, there must be an overall level of substantial worsening in non-target disease such that, even in presence of stable disease or partial response in TLs, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more NTLs is usually not sufficient to qualify for unequivocal progression status.

G 4.4 New lesions

Details of any new lesions will also be recorded with the date of assessment. The presence of one or more new lesions is assessed as progression.

A lesion identified at a follow-up assessment in an anatomical location that was not scanned at pre-dose is considered a new lesion and will indicate disease progression.

The finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour.

If a new lesion is equivocal, for example because of its small size, the treatment and tumour assessments should be continued until the new lesion has been confirmed. If repeat scans confirm there is a new lesion, then the progression date should be declared using the date of the initial scan when the new lesion first appeared.

G 4.5 Symptomatic deterioration

Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy.

Patients with 'symptomatic deterioration' requiring discontinuation of treatment without objective evidence of disease progression at that time should continue to undergo tumour assessments where possible until objective disease progression is observed.

G 4.6 Evaluation of overall visit response

The overall visit response will be derived using the algorithm shown in Table G4.

Table G4 Overall visit response

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	NA	No	CR
CR	Non CR/Non PD	No	PR
CR	NE	No	PR
PR	Non PD or NE	No	PR
SD	Non PD or NE	No	SD
NE	Non PD or NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR, complete response; NA, Not applicable (only relevant if there were no non-target lesions at pre-dose); NE, not evaluable; PD, progression of disease, PR, partial response, SD, stable disease

G 5 Confirmation of progression

In HUDSON, a scan is required for confirmation of progression; the confirmatory scan should occur no earlier than 4 weeks after the prior assessment of PD in the absence of clinical deterioration.

Progression in the confirmatory scan would be considered confirmed if the following criteria are met:

- ≥20% increase in the sum diameters of TLs compared with the nadir at 2 consecutive visits
- And/or significant progression (worsening) of NTLs or new lesions at the confirmatory PD time-point compared with the first timepoint where progression of NTLs or new lesions identified
- And/or additional new unequivocal lesions at the confirmatory PD time-point compared with the first timepoint new lesions identified.

In the absence of significant clinical deterioration, the investigator should continue study treatment until progression is confirmed.

If progression is not confirmed, then the patient should continue on study treatment and on treatment assessments.

If a patient discontinues treatment (and/or receives a subsequent cancer therapy) prior to progression, then the patient should still continue to be followed until confirmed objective disease progression.

G 6 Specification for radiological imaging

These notes are recommendations for use in clinical studies. The use of standardised protocols for CT and MRI allows comparability both within and between different studies, irrespective of where the examination has been undertaken.

G 6.1 CT scan

CT scans of the chest and abdomen (and pelvis when indicated) should be contiguous throughout all the anatomic region of interest.

The most critical CT image acquisition parameters for optimal tumour evaluation using RECIST 1.1 are anatomic coverage, contrast administration, slice thickness, and reconstruction interval.

(a) Anatomic coverage: Optimal anatomic coverage for most solid tumours is the chest, abdomen and pelvis. Coverage should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients. Because a lesion later identified in a body part not scanned at pre-dose would be considered as a new lesion representing disease progression, careful consideration should be given to the extent of imaging coverage at pre-dose and at subsequent follow-up timepoints. This will enable better consistency not only of tumour measurements but also identification of new disease.

(b) IV contrast administration: Optimal visualisation and measurement of metastases in solid tumours requires consistent administration (dose and rate) of IV contrast as well as timing of scanning. Typically, most abdominal imaging is performed during the portal venous phase and (optimally) about the same time frame after injection on each examination. An adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient. It is very important that the same technique be used at pre-dose and on follow-up examinations for a given patient. For patients who develop contraindications to contrast after pre-dose contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) should be performed should also be based on the tumour type, anatomic location of the disease and should be optimised to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be

considered not evaluable from that point forward. Care must be taken in measurement of target lesions on a different modality and interpretation of non-target disease or new lesions, since the same lesion may appear to have a different size using a new modality. Oral contrast is recommended to help visualise and differentiate structures in the abdomen.

If iodine contrast media is medically contraindicated at pre-dose or at any time during the course of the study, then the recommended methods are: CT thoracic (chest) examination without contrast and abdominal (and pelvis) MRI with contrast. If MRI cannot be performed, then CT without IV contrast is an option for the thorax and abdomen (and pelvis) examination. For brain imaging, MRI with IV contrast is the preferred method.

(c) Slice thickness and reconstruction interval: It is recommended that CT scans be performed at 5 mm contiguous slice thickness and this guideline presumes a minimum 5 mm thickness in recommendations for measurable lesion definition. Exceptionally, particular institutions may perform medically acceptable scans at slice thicknesses greater than 5 mm. If this occurs, the minimum size of measurable lesions at pre-dose should be twice the slice thickness of the pre-dose scans.

All window settings should be included in the assessment, particularly in the thorax where lung and soft tissue windows should be considered. When measuring lesions, the TL should be measured on the same window setting for repeated examinations throughout the study. All images from each examination should be included in the assessment and not 'selected' images of the apparent lesion.

G 6.2 MRI scan

MRI has excellent contrast, spatial and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity and measurement. Furthermore, the availability of MRI is variable globally. The modality used at follow-up should be the same as was used at pre-dose and the lesions should be measured/assessed on the same pulse sequence. Generally, axial imaging of the abdomen and pelvis with T1 and T2 weighted imaging along with gadolinium-enhanced imaging should be performed. The field of view, matrix, number of excitations, phase encode steps, use of fat suppression and fast sequences should be optimised for the specific body part being imaged as well as the scanner utilised. It is beyond the scope appendix to prescribe specific MRI pulse sequence parameters for all scanners, body parts and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques if possible.

For these reasons, CT is the imaging modality of choice.

G 6.3 CT portion of PET/CT scans

At present, low dose or attenuation correction CT portions of a combined positron emission tomography/CT are of limited use in anatomically based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for tumour measurements by RECIST 1.1. In exceptional situations, if a site can document that the CT performed as part of a PET/CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the PET/CT can be used for RECIST 1.1 measurements. However, this is not recommended because the PET portion of the CT introduces additional data that may bias an investigator if it is not routinely or serially performed.

Appendix H Toxicity management guidelines for durvalumab

The most current version of these guidelines is maintained within the Site Master File.

Comparison Table of Changes to the Protocol Version 14.0

Several sections of the protocol have been updated or are new. All changes are summarised in the table below. Typographical and formatting changes are not documented in the table of changes.

Previous Version: 13.0, 14 December 2024
New Version: 14.0, 09 October 2024

- Changes are described under the **Core Clinical Study Protocol** Section heading where the main change is made. Where additional sections have been updated for the same changes, these sections are specified in the column 'comments/explanation/reasons for amendment'. Restructuring of existing information and deletion of duplicate text between sections is not documented in the table of changes. Details are included in the **Core Clinical Study Protocol** version history for protocol version 14.0.
- The version number and date of all individual modules were revised in line with the Core Clinical Study Protocol for the HUDSON study; additional changes **documented solely in individual modules** are described separately after the Core Clinical Study Protocol changes.

Previous and New Wording in Track Change Modus (new text in coloured font, deleted text in ~~scored through font~~)	**New Wording**	**Comments/ Explanation/ Reasons for Amendment**
Core CSP **Section 4.4 End of study definition**		
(…) Patients who are receiving treatment following ~~the data cut-off~~database lock for the final analysis can either choose to discontinue from the study or, where the investigator believes patients are gaining clinical benefit, patients may continue to receive study treatment following discussion with, and approval from~~ the sponsor.~~, the sponsor in accordance with Section 8.3.14. All patients will receive follow-up care in accordance with standard local clinical practice. For patients who do continue to receive treatment beyond the time of the final ~~data cut-off~~database lock, investigators will continue to report all non-serious adverse events (AEs) and serious adverse events (SAEs), pregnancy, and overdose until 90 days after the last dose of study treatment, in accordance with Section 8.4.1 using paper forms. Additionally, any SAE that is ongoing at the time of the final ~~data cut-off~~database lock must be followed up to resolution unless the event is considered by the investigator to be unlikely to resolve, or the patient is lost to follow-up. See Appendix A 6 for guidelines for the dissemination of study results.	(…) Patients who are receiving treatment following database lock for the final analysis can either choose to discontinue from the study or, where the investigator believes patients are gaining clinical benefit, patients may continue to receive study treatment following discussion with, and approval from, the sponsor in accordance with Section 8.3.14. All patients will receive follow-up care in accordance with standard local clinical practice. For patients who do continue to receive treatment beyond the time of the final database lock, investigators will continue to report all non-serious adverse events (AEs) and serious adverse events (SAEs), pregnancy, and overdose until 90 days after the last dose of study treatment, in accordance with Section 8.4.1 using paper forms. Additionally, any SAE that is ongoing at the time of the final database lock must be followed up to resolution unless the event is considered by the investigator to be unlikely to resolve, or the patient is lost to follow-up. See Appendix A 6 for guidelines for the dissemination of study results.	Updated "data cut-off" to "database lock" throughout this section and updated to state non-serious AEs would also be collected in patients who continue to receive treatment after database lock.

Previous and New Wording in Track Change Modus (new text in coloured font, deleted text in ~~scored through font~~)	**New Wording**	**Comments/ Explanation/ Reasons for Amendment**
Core CSP **Section 7.2 Lost to follow-up**		
Before a patient is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the patient or next of kin ~~by eg, repeat~~(where possible, 2 attempts will be made using either telephone calls, certified letter to the patient´s last known mailing address or local equivalent methods~~.~~). These contact attempts should be documented in the patient's medical record.	Before a patient is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the patient or next of kin (where possible, 2 attempts will be made using either telephone calls, certified letter to the patient´s last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.	Updated to state 2 attempts should be made when attempting to contact a patient who has missed a scheduled site visit.
Core CSP **Section 8.3.2 Time period and frequency for collecting AE and SAE information**		
(…) For patients who continue to receive intervention after final database lock, investigators will continue to report all non-serious AEs and SAEs to AstraZeneca Patient Safety until 90 days after study intervention is discontinued (see Section 4.4). (…)	(…) For patients who continue to receive intervention after final database lock, investigators will continue to report all non-serious AEs and SAEs to AstraZeneca Patient Safety until 90 days after study intervention is discontinued (see Section 4.4). (…)	Updated to describe the collection of non-serious AEs and SAEs in patients who continue to receive study treatment after final database lock and are later discontinued from study treatment.

Previous and New Wording in Track Change Modus (new text in coloured font, deleted text in ~~scored through font~~)	**New Wording**	**Comments/ Explanation/ Reasons for Amendment**
Core CSP **Section 8.3.13, Safety data to be collected following the final database lock**		
8.3.13 Safety data to be collected following the ~~final~~ database lock of each module~~data cut-off of each module~~ For patients continuing to receive treatment after ~~final~~ database lock of each module~~data and database closure of each module~~, it is recommended that the patients continue the scheduled site visits and Investigators monitor the patient's safety laboratory results prior to and periodically during treatment in order to manage AEs in accordance with the durvalumab Dose Modification and Toxicity Management Guidelines (see Section 8.4.5) and the specific toxicity management guidelines for each study drug as described in appropriate module. All data post database lock ~~the final data cut-off and database closure~~ for each module will be recorded in the patient notes but, with the exception of non-serious AEs and SAEs, will not otherwise be reported for the purposes of this study. All non-serious AEs and SAEs that occur in patients still receiving treatment (or within the 90 days following the last dose of treatment) post the database lock ~~final data cut-off and database closure~~for each module must be reported as detailed in Section 8.4.1.	8.3.13 Safety data to be collected following the final database lock For patients continuing to receive treatment after final database lock, it is recommended that the patients continue the scheduled site visits and Investigators monitor the patient's safety laboratory results prior to and periodically during treatment in order to manage AEs in accordance with the durvalumab Dose Modification and Toxicity Management Guidelines (see Section 8.4.5) and the specific toxicity management guidelines for each study drug as described in appropriate module.	Title of the section was updated along with corresponding updates to the text.
Core CSP **Section 8.3.14 Continued access to study intervention after the end of the study**		
AstraZeneca will continue to supply study treatment to patients after final database lock while, in the opinion of the Investigator, the participant is benefiting. Patients should be followed according to institution's standard of care assessments or accordance with standard local clinical practice. No further data collection is required except reporting of AEs, SAEs, AESIs, overdoses, pregnancies, medication error, drug abuse and drug misuse.	AstraZeneca will continue to supply study treatment to patients after final database lock while, in the opinion of the Investigator, the participant is benefiting. Patients should be followed according to institution's standard of care assessments or accordance with standard local clinical practice. No further data collection is required except reporting of AEs, SAEs, AESIs, overdoses, pregnancies, medication error, drug abuse and drug misuse.	Section added to describe the continued supply of study treatment by the Sponsor to patients after data cut-off.

Previous and New Wording in Track Change Modus (new text in coloured font, deleted text in ~~scored through font~~)	**New Wording**	**Comments/ Explanation/ Reasons for Amendment**
In the event that product development reaches a point where alternative product supply options become available, then these alternative product supply options will be discussed by AstraZeneca with the Investigator. AstraZeneca will work with the Investigator to transition the patient(s) to alternative supply, unless impossible for local reasons. In the event that a roll-over or safety extension study is available, patient(s) currently receiving treatment may then be transitioned to such a study, and the current study may reach its end. The roll-over or extension study would ensure treatment continuation with visit assessments per its protocol, as applicable. Any patient who would be eligible to move to such a study would be given a new informed consent, as applicable. In the event that AstraZeneca terminates further development of the study intervention, AstraZeneca will continue to supply study intervention where possible, however the supply may become unavailable. AstraZeneca will notify Investigators in advance if supply of study intervention must be discontinued.	In the event that product development reaches a point where alternative product supply options become available, then these alternative product supply options will be discussed by AstraZeneca with the Investigator. AstraZeneca will work with the Investigator to transition the patient(s) to alternative supply, unless impossible for local reasons. In the event that a roll-over or safety extension study is available, patient(s) currently receiving treatment may then be transitioned to such a study, and the current study may reach its end. The roll-over or extension study would ensure treatment continuation with visit assessments per its protocol, as applicable. Any patient who would be eligible to move to such a study would be given a new informed consent, as applicable. In the event that AstraZeneca terminates further development of the study intervention, AstraZeneca will continue to supply study intervention where possible, however the supply may become unavailable. AstraZeneca will notify Investigators in advance if supply of study intervention must be discontinued.	

Previous and New Wording in Track Change Modus (new text in coloured font, deleted text in ~~scored through font~~)	**New Wording**	**Comments/ Explanation/ Reasons for Amendment**
Core CSP **Section 8.4.1 Reporting of serious adverse events**		
(…) If the EDC system is not available, then the investigator or other study site staff reports a SAE to the appropriate AstraZeneca representative by telephone followed by completion of a paper SAE form. The AstraZeneca representative will advise the investigator/study site staff how to proceed. The AstraZeneca representative will advise the investigator/study site staff how to proceed. In the European Union, the Sponsor will comply with safety reporting requirements and procedures as described in the European Clinical Trials Regulation (EU) No 536/2014. All Suspected Unexpected Serious Adverse Reactions (SUSARs) to the investigational medicinal product will be reported to the EudraVigilance database within the required regulatory timelines. Non-serious AEs and SAEs will be recorded by the treating physician from the time the patient signs informed consent and will continue throughout the program until the end of the post-trial access period or until consent has been withdrawn. Reports of pregnancy, overdose, medication error, drug abuse, and drug misuse with associated non-serious AEs and SAEs will be reported to the AZ DES within the same timelines specified for SAEs. For further guidance on the definition of a SAE, see Appendix B of the CSP.	(…) If the EDC system is not available, then the investigator or other study site staff reports a SAE to the appropriate AstraZeneca representative by telephone followed by completion of a paper SAE form. The AstraZeneca representative will advise the investigator/study site staff how to proceed. The AstraZeneca representative will advise the investigator/study site staff how to proceed. In the European Union, the Sponsor will comply with safety reporting requirements and procedures as described in the European Clinical Trials Regulation (EU) No 536/2014. All Suspected Unexpected Serious Adverse Reactions (SUSARs) to the investigational medicinal product will be reported to the EudraVigilance database within the required regulatory timelines. Non-serious AEs and SAEs will be recorded by the treating physician from the time the patient signs informed consent and will continue throughout the program until the end of the post-trial access period or until consent has been withdrawn. Reports of pregnancy, overdose, medication error, drug abuse, and drug misuse with associated non-serious AEs and SAEs will be reported to the AZ DES within the same timelines specified for SAEs. For further guidance on the definition of a SAE, see Appendix B of the CSP.	Addition of text clarifying reporting of SAEs, EU CTR SUSAR reporting process, and reporting of non-serious AEs and SAEs until the end of the post-trial access period.

Previous and New Wording in Track Change Modus (new text in coloured font, deleted text in ~~scored through font~~)	**New Wording**	**Comments/ Explanation/ Reasons for Amendment**
Core CSP **Section 9.4.2 General considerations**		
(…) Further survival data will continue to be collected until the planned database lock for a module, which can occur either 12 months after the last patient has started treatment or when 75% of the patients have died. Limited data for any patients who are ongoing on study treatment in the module will be collected following the data cut-off for the module CSR (refer to the schedule of activities per module), and the survival follow-up will end for the module. ~~The safety data for ongoing patients following the data cut-off for the module CSR will be listed in a modular CSR addendum or final study CSR.~~ (…)	(…) Further survival data will continue to be collected until the planned database lock for a module, which can occur either 12 months after the last patient has started treatment or when 75% of the patients have died. Limited data for any patients who are ongoing on study treatment in the module will be collected following the data cut-off for the module CSR (refer to the schedule of activities per module), and the survival follow-up will end for the module. (…)	Text describing the reporting of safety data in ongoing patients following the data cut-off in a modular CSR addendum or final CSR was deleted.
Additional changes solely documented in individual modules		
Modules 8, 11 **Section 2.2.1.3, AZD6738 monotherapy safety data**		
(…) Anaemia, thrombocytopenia, and neutropenia (including febrile neutropenia), nausea, vomiting, diarrhoea, and fatigue/asthenia have been reported when AZD6738 is used as monotherapy and when used in combination with durvalumab. (…)	(…) Anaemia, thrombocytopenia, and neutropenia (including febrile neutropenia), nausea, vomiting, diarrhoea, and fatigue/asthenia have been reported when AZD6738 is used as monotherapy and when used in combination with durvalumab. (…)	New identified risks.
Modules 3, 10 **Section 2.2.2.2, AZD6738 data**		
(…) Anaemia, thrombocytopenia, and neutropenia (including febrile neutropenia), nausea, vomiting, diarrhoea, and fatigue/asthenia have	(…) Anaemia, thrombocytopenia, and neutropenia (including febrile neutropenia), nausea, vomiting, diarrhoea, and fatigue/asthenia have	New identified risks.

<table>
<tr><th>Previous and New Wording in Track Change Modus (new text in coloured font, deleted text in ~~scored through font~~)</th><th>New Wording</th><th>Comments/ Explanation/ Reasons for Amendment</th></tr>
<tr><td>been reported when AZD6738 is used as monotherapy and when used in combination with olaparib or durvalumab.

(…)</td><td>been reported when AZD6738 is used as monotherapy and when used in combination with olaparib or durvalumab.

(…)</td><td></td></tr>
<tr><td colspan="3">Module 9
Section 2.2.3.1, Emerging data from module 3 of HUDSON</td></tr>
<tr><td>(…)

Anaemia, thrombocytopenia, and neutropenia (including febrile neutropenia), nausea, vomiting, diarrhoea, and fatigue/asthenia have been reported when AZD6738 is used as monotherapy and when used in combination with durvalumab.

(…)</td><td>(…)

Anaemia, thrombocytopenia, and neutropenia (including febrile neutropenia), nausea, vomiting, diarrhoea, and fatigue/asthenia have been reported when AZD6738 is used as monotherapy and when used in combination with durvalumab.

(…)</td><td>New identified risks.</td></tr>
<tr><td colspan="3">Modules 3, 9, 10
Table 2, Study drug</td></tr>
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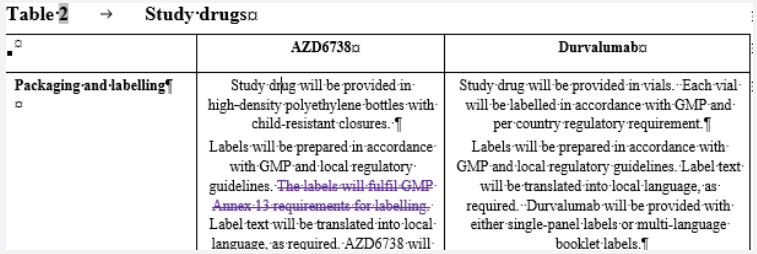
Table 2 → Study drugs
 
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 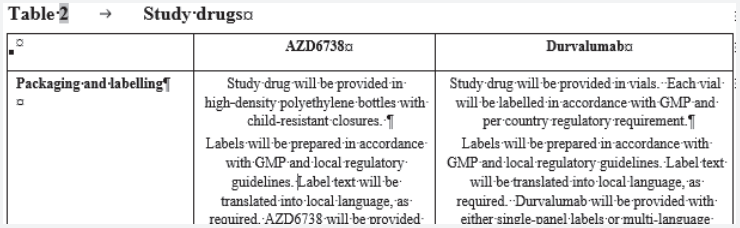
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Previous and New Wording in Track Change Modus (new text in coloured font, deleted text in ~~scored through font~~)	**New Wording**	**Comments/ Explanation/ Reasons for Amendment**
Modules 3, 9, 10 **Section 6.5.2, Effect of AZD6738 on other drugs; Section 11 AZD6738 drug-drug interactions**		
AZD6738 is an ~~potential~~inducer of CYP1A2, CYP2B6, and CYP3A4 and ~~a potential inhibitor~~showed weak inhibition of CYP1A2, CYP2C8 and CYP2C9. Caution should be applied with co-administration of drugs that are either completely metabolised by CYP3A4 and/or CYP1A2 or CYP2C8 or CYP2C9, or that are substrates of CYP3A4 and/or CYP1A2, CYP2C8 and CYP2C9 and also have a narrow therapeutic index.	AZD6738 is an inducer of CYP1A2, CYP2B6, and CYP3A4 and showed weak inhibition of CYP1A2, CYP2C8 and CYP2C9. Caution should be applied with co-administration of drugs that are either completely metabolised by CYP3A4 and/or CYP1A2 or CYP2C8 or CYP2C9, or that are substrates of CYP3A4 and/or CYP1A2, CYP2C8 and CYP2C9 and also have a narrow therapeutic index.	Section revised to add updated nonclinical PK and drug metabolism information.
Modules 8, 11 **Section 6.5.2, Drug-drug interaction between AZD6738 and other drugs; 11, AZD6738 drug-drug interactions**		
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Modules 3, 8, 9, 10, 11 **Section 8.4.1, Reporting of serious adverse events**		
Please refer to the core protocol. Any myeloid malignancies (ie., MDS and/or AML) should be reported whenever this has been observed in the follow-up of the patients.	Please refer to the core protocol. Any myeloid malignancies (ie., MDS and/or AML) should be reported whenever this has been observed in the follow-up of the patients.	Added reporting requirements for patients with MDS and/or AML.
Modules 8, 11 **Section 8.4.5 Management of study drug-related toxicities**		
(…) If a patient develops severe haematologic toxicity or blood transfusion dependence, treatment with ceralasertib should be interrupted and appropriate haematologic testing should be initiated.	(…) If a patient develops severe haematologic toxicity or blood transfusion dependence, treatment with AZD6738 should be interrupted and appropriate haematologic testing should be initiated.	Precautions for use for the new potential risk.

Previous and New Wording in Track Change Modus (new text in coloured font, deleted text in ~~scored through font~~)	**New Wording**	**Comments/ Explanation/ Reasons for Amendment**
If the blood parameters remain clinically abnormal after 4 weeks of ceralasertib dose interruption, bone marrow analysis and/or blood cytogenetic analysis are recommended. If myeloid malignancies are confirmed whilst on treatment with ceralasertib, it is recommended that ceralasertib should be discontinued and the patient be treated appropriately. AEs of myeloid malignancies should be monitored by conventional AE collection and reporting, additionally any cases should be reported after the 30-day follow-up period irrespective of Investigator causality. (…) **Haematologic** Patients with suspected or with indications of MDS and/or AML must have the dose of AZD6738 stopped under all circumstances, and evidence of AML/MDS should be ruled out. Further treatment can only be accepted after discussion and agreement with the sponsor.	If the blood parameters remain clinically abnormal after 4 weeks of AZD6738 dose interruption, bone marrow analysis and/or blood cytogenetic analysis are recommended. If myeloid malignancies are confirmed whilst on treatment with AZD6738, it is recommended that AZD6738 should be discontinued and the patient be treated appropriately. AEs of myeloid malignancies should be monitored by conventional AE collection and reporting, additionally any cases should be reported after the 30-day follow-up period irrespective of Investigator causality. (…) **Haematologic** Patients with suspected or with indications of MDS and/or AML must have the dose of AZD6738 stopped under all circumstances, and evidence of AML/MDS should be ruled out. Further treatment can only be accepted after discussion and agreement with the sponsor.	
Module 3, 9, 10 **Section 8.4.5.2, Management of AZD6738-related toxicities**		
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Clinical Study Protocol

Drug Substance	Umbrella study
Study Code	D6185C00001 (HUDSON)
Version	14.0
Date	09 October 2024

Appendix I

Module 1: Durvalumab plus olaparib

An Open-Label, Multi-Drug, Biomarker-Directed, Multi-Centre Phase II Umbrella Study in Patients with Non-Small Cell Lung Cancer, who Progressed on an Anti-PD-1/PD-L1 Containing Therapy (HUDSON)

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

Regulatory Agency Identification Numbers:

EudraCT number: 2017-002208-28

EU CT number: 2023-509004-15-00

IND number: 138050

VERSION HISTORY

Version 14.0, 09 October 2024
Key amendments and rationale for changes: The version number of this module has been revised in line with the other modules in the HUDSON study; however, no changes have been made to this module.

Version 13.0, 14 December 2023
Key amendments and rationale for changes: **Front page:** EU CT number has been added in line with the core CSP.

Version 12.0, 01 March 2023
Key amendments and rationale for changes: The version number of this module has been revised in line with the other modules in the HUDSON study; however, no changes have been made to this module.

Version 11.0, 16 August 2022
Key amendments and rationale for changes: The version number of this module has been revised in line with the other modules in the HUDSON study; however, no changes have been made to this module.

Version 10.0, 12 April 2022
Key amendments and rationale for changes: **Table 1, schedule of activities:** Addition of footnote to clarify the activities for patients continuing on study treatment after the data cut-off for the module clinical study report.

Figure 1, study design: Footnote added to clarify survival follow-up of screen failures and optional patient treatment re-allocation to a second treatment cohort are no longer required as of implementation of protocol v10.0.

Section 2.2, background: Reference to approval of durvalumab for the treatment of urothelial carcinoma in the US removed due to voluntary withdrawal of this indication in this country. Text also added to clarify the weight-based regimen (10 mg/kg every 2 weeks) is approved for urothelial carcinoma.

Section 2.2.1.2, durvalumab data: Number of patients treated with durvalumab updated to align with durvalumab IB Edition 17.

Section 5.3.1, restrictions applicable to durvalumab; Table 4, supportive medication: Text added to provide guidance for the use and timing of authorised and approved COVID-19 vaccines, to align with the COVID-19 vaccination guidance letter (dated 24 February 2021) provided to sites.

Table 6, schedule of activities for patients re-allocated to second on-treatment period (Module 1): Footnote added to clarify from implementation of protocol v10.0, optional treatment re-allocation of patients is no longer applicable. Related sentence also included in Section 7 text.

Section 8.4.6, adverse events of special interest: Pneumonitis changed from 'important potential risk' to 'potential risk' to align with olaparib IB Edition 21.

Version 9.0, 14 May 2021

Key amendments and rationale for changes:

The version number of this module has been revised in line with the other modules in the HUDSON study; however, no changes have been made to this module.

Version 8.0, 11 September 2020

Key amendments and rationale for changes:

Removal of web link to the durvalumab toxicity management guidelines as this website has been decommissioned. The toxicity management guidelines will instead be provided to sites: Section 6.2.1, Section 6.6, and Section 8.4.5.1.

Section 8.4.6 Adverse events of special interest: MDS/AML has been reclassified as an important identified risk in olaparib IB Edition 19, so the text has been updated accordingly.

Version 7.0, 21 May 2020

Key amendments and rationale for changes:

Figure 2 (study flow diagram): this figure has been removed from all modules and a cross reference added to the same figure in the core protocol instead. Change made to limit the number of modules requiring updating during a protocol amendment whenever a new module is added.

Section 2.2 Background: Updates to the registered use and approvals for durvalumab and olaparib.

Section 2.2.2.2 Olaparib and **Section 4.3.2 Justification for dose**: Updates to align with olaparib IB Edition 18.

Section 6.2.1 Durvalumab preparation and handling: Clarification that if the final product is stored at both refrigerated and ambient temperatures, the total time should not exceed 24 hours.

Sections 6.4 Treatment compliance and **6.6 Dose modification and discontinuation:** Clarification that dose reductions are not permitted for durvalumab.

Version 6.0, 05 November 2019

Key amendments and rationale for changes:

Table 1 Schedule of Activities: Footnote added that ad-hoc collection of survival status may be requested for OS analyses

Section 2.2 Background: Text updated to align with Edition 17 of the olaparib IB and Edition 15 of the durvalumab IB.

Figure 2 Study flow diagram: Updated to reflect the addition of Modules 6 and 7.

Section 4.3.1 Justification of durvalumab dose: Correction of typographical errors and to align with Edition 15 of the durvalumab IB.

Section 6.2.1 Durvalumab preparation and handling: Change to the window around the duration of durvalumab infusion to ±15 minutes. The previous window of ±5 minutes was considered too restrictive.

Section 6.4 Treatment compliance: Instructions on how to record treatment compliance with olaparib updated for clarity.

Table 3 Prohibited medications: Information on the rationale for the prohibition of EGFR TKIs added.

Section 8.2.1.2 Other safety assessments: Cross references to Tables 1 and 6 added.

Section 8.4.6 Adverse events of special interest: New section created for the AESIs for clarity. Changes made to the text to align with changes being made in the core protocol.

Version 5.0, 19 March 2019

Key amendments and rationale for changes:

Table 1 Schedule of Activities – Treatment intervention period (Module 1):

- Clarified that tumour evaluation scans are required until objective disease progression, up to and including the 90-day safety follow-up period.
- Updated in line with the core protocol, to replace modified RECIST 1.1 with RECIST 1.1, to ensure comparability with other NSCLC study results. Updated for consistency across all modules of the study.

Figure 1 Study design: Updated to clarify that patients with locally advanced disease are included, and to specify ctDNA at pre-screening.

Section 2 Introduction and **Section 4.1 Overall design:** Amended in line with inclusion criterion 5 in the core clinical study protocol (CSP), which clarified the required prior treatment in response to questions from investigators. According to the study's main objective, patients must have had disease progression on a prior anti-PD-1/PD-L1 therapy. The patient must have also received a prior platinum doublet though it is not required to have had disease progression whilst receiving treatment with the platinum doublet therapy.

Section 2.1 Study rationale: Clarification that there is currently no established therapy for patients who have developed resistance to PD-1/PD-L1 and platinum-doublet therapies.

Section 2.2 Background: Indication text updated to reflect status of approvals for durvalumab (IB Edition 14, 11 February 2019) and olaparib (IB Edition 16 29 January 2019).

Section 2.2.1.1 Overview of durvalumab: Indication text updated to reflect status of approvals for durvalumab (IB Edition 14, 11 February 2019).

Section 2.2.1.2 Durvalumab data: PACIFIC overall survival data and Study CD-ON-MEDI4736-1108 efficacy data updated in line with the IB for durvalumab (IB Edition 14, 11 February 2019).

Section 2.2.2.1 Overview of olaparib: Indication text updated to reflect status of approvals for olaparib (IB Edition 16, 29 January 2019).

Section 2.2.2.2 Olaparib data: Study information and exposure data updated in line with IB for olaparib (IB Edition 16, 29 January 2019).

Section 2.3.1.1 Olaparib in combination benefit/risk: Text updated in line with IB for olaparib (IB Edition 16, 29 January 2019).

Figure 2 Study flow diagram: Footnote added to specify that per protocol version 3.0, Module 4 (durvalumab + vistusertib) is closed to recruitment.

Section 5.3.1 Restrictions applicable to durvalumab: Noted that topical corticosteroids are permitted.

The following sections have been updated in line with the core durvalumab Clinical Study Protocol (CSP), in which the Toxicity Management Guidelines (TMGs) for durvalumab have been removed from the main body of the CSP template and moved to a standalone annex. TMG versioning will be independent of the protocol allowing for consistency across the durvalumab clinical development programme. Updated for consistency across all modules of the study.

- Section 6.2.1 Durvalumab preparation and handling
- Section 6.6 Dose modification and discontinuation
- Section 8.4.5.1 Management of durvalumab-related toxicities

Section 6.2.1 Durvalumab preparation and handling: Updated for clarity and alignment with product insert.

Section 6.2.3 Study drug administration: Updated in line with the core protocol, to replace modified RECIST 1.1 with RECIST 1.1, to ensure comparability with other NSCLC study results. **Section 6.4 Treatment compliance, Section 6.6 Dose modification and discontinuation** and **Section 8.4.5 Management of study-drug related toxicities:** Clarified that dose reductions are not allowed for durvalumab without prior agreement with the study physician. **Section 6.6 Dose modification and discontinuation:** Section header amended for consistency with other modules; text changed from 'temporary discontinuation' to 'treatment interruption' for clarity. **Table 6 Schedule of Activities for patients re-allocated to second on-treatment period (Module 1):** Updated to clarify that informed consent and screening period to confirm eligibility for re-allocation will be performed within 28 days before dosing and to cross refer to the eligibility criteria in Table 1 of the core CSP.
Version 4.0, 26 October 2018
Updated version number to keep in line with changes made in the core CSP. No other changes were made in this appendix.
Version 3.1, 31 July 2018
Table 1 Schedule of Activities: Update to the durvalumab ADA sampling schedule in response to a request from the FDA. Sampling is still required pre-dose on Cycle 1 Day 1 and Cycle 2 Day 1, but is now also subsequently required Q12W within the first year and Q24W in the second year of treatment. Addition of a ±7 day window around the study discontinuation and follow-up visits. Removal of WHO/ECOG assessments: these will now only be performed at screening to reduce the burden on sites. **Section 2.2 Background:** Updates to durvalumab background information in light of emerging data. **Figure 2 Flow diagram:** Updated to reflect the addition of Module 5 to the protocol. **Section 4.1 Overall design:** correction of the window allowed for durvalumab infusion from ±3 days to ±2 days to align with the rest of the protocol. **Section 5.2 Exclusion criteria (Module 1-specific):** Addition of exclusion I-8 Inability to swallow the formulated product.

Section 5.3.1 Restrictions applicable to durvalumab: Amended to extend the period patients should not receive live vaccines to 180 days after the last dose of study drug. Updated for consistency across all modules of the study.

Section 6.2.2 Olaparib preparation and handling: Allowing a ±2 hour window around the dosing of olaparib to improve the logistics for patients.

Section 6.2.3 Study drug administration and Section 6.6 dose modification: Text moved from the module to the core protocol and amended to allow patients to continue receiving treatment with monotherapy if, in the opinion of the treating physician, they are deriving benefit.

Table 3 Prohibited medications: Updated to align with updated exclusion criteria in the core protocol.

Table 6 Schedule of Activities for patients re-allocated to second on treatment period: Addition of a ±7 day window around the study discontinuation and follow-up visits. Removal of WHO/ECOG assessments: these will now only be performed at screening to reduce the burden on sites.

Version 2.0, 26 February 2018

Key amendments and rationale for changes:

IND number updated following advice from the FDA to conduct HUDSON under its own IND, which cross references IND 119833.

Table 1 Schedule of activities and **Table 6 Schedule of Activities for patients re-allocated to second on-treatment period:** Pregnancy testing is required on day 1 of every cycle only. Items deleted for C1D15 and C2D15.

Figure 1 Study design: For patients who are re-allocated to a second treatment within HUDSON, the "screening assessments as per schedule of assessments in the treatment specific module" was corrected to state "as per schedule of assessments **in the core protocol**".

Figure 2 Study Flow Diagram: Based on observations from other studies exploring the hypothesis of TORC1/2 inhibition, *TSC1* and *TSC2* have been removed as biomarkers of interest in HUDSON.

2.2.1 Durvalumab: Background information added in line with the durvalumab IB Edition 12.

2.2.2 Olaparib data: Additional background information included on the use of olaparib and durvalumab in clinical studies and update on marketing authorisations.

4.3.1 Justification for durvalumab dose: information added on dose justification in line with the durvalumab IB Edition 12.

5.1 Inclusion criteria: Cohort names were corrected

5.2 Exclusion criteria:

- Exclusion criterion I-2, clarification that the Cockcroft-Gault equation will be utilised at screening to determine eligibility, considering the Cockcroft-Gault equation is a more reliable indicator of renal function than creatinine alone. Patients with a creatinine clearance ≤50 mL/min, calculated by the Cockcroft-Gault equation, are not eligible.
- The exclusion criterion on the timing of blood transfusion was labelled I-2 by mistake. It has been corrected to be I-7.

5.3 Lifestyle restrictions:

- Blood donation guidance updated to be in line with the new durvalumab IB Edition 12. Section also revised to 'refer to section 5.3 of the core protocol'.
- Information about reproduction restrictions is included within the core protocol to ensure consistency in reproduction and contraception requirements across each module. Patients will be required to adopt birth control methods (and avoid the donation of sperm) from screening until 6 months after the last dose of study drug.

6.2.3 Study drug administration: Patients allocated to a biomarker matched cohort who, in the opinion of the treating physician would benefit from continued treatment with olaparib whilst durvalumab is discontinued, may continue treatment with prior approval from the study physician. This text was also added to section **6.6 Dose modification** for clarity

6.6 Dose modification: Clarification of dose modification rules, including:

- If patients'body weight falls ≤30 kg during the study, (s)he will be withdrawn from the study treatment unless (s)he derives some clinical benefit according to the treating physician. This text was also added to section **6.2.1 Durvalumab preparation and handling** for clarity.
- Management of dose interruptions of durvalumab and olaparib.

Table 6 Schedule of activities for re-allocation of treatment: Footnote added to clarify that eligibility criteria for both core CSP and this module are applicable.

8.4.5.2 Management of olaparib-related toxicities and **Table 7 Management of anaemia:** Updated guidelines on the management of haematological toxicities based on new information received. Clarification that platelet transfusions are allowed and correction of inconsistency in the management of CTCAE Grade 3 to 4 neutropenia, leukopenia and thrombocytopenia

References: Provided the correct reference to Skoulidis et al. (2017)

Version 1.0, 05 September 2017
Initial Creation

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

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1. PROTOCOL SUMMARY

1.1 Schedule of Activities (SoA)

The Schedule of Activities (SoA) for the on-treatment period for Module 1 is shown in Table 1 below, and for the optional re-allocated second on-treatment period in Section 7, Table 6. For the SoA for the pre-screening and main-screening visits, please refer to the core protocol.

Table 1 Schedule of Activities – Treatment intervention period (Module 1)

	C1 28 days Weeks 1-4		**C2** 28 days Weeks 5-8		**C3** 28 days Weeks 9-12	**C4** 28 days Weeks 13-16	**C5 – etc** All cycles 28 days	**Study drug disc.** (28 days after study drug disc.)	**Safety follow-up** (90 days after study drug disc.)	**Survival follow up**	**Notes**
Week	**1**	**3**	**5**	**7**	**9**	**13**	**17, 21, 25, 29 etc**				
Cycle day	**1**	**15**	**1**	**15**	**1**	**1**	**1**				
Window (days)	**0**[a]	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±7**	**±7**	**±7**	
Study procedures[c]											
Physical examination	X	X	X	X	X	X	X	X			Section 8.2.2 (core protocol)
Vital signs	X	X	X	X	X	X	X	X			Section 8.2.3 (core protocol)
ECG	X	As clinically indicated									Section 8.2.4 (core protocol)
Concomitant medications	X	X	X	X	X	X	X	X			Section 6.5
Laboratory assessments[c]											
Clinical chemistry	X	X	X	X	X	X	X	X			Section 8.2.1 (core protocol). If screening laboratory assessments are performed within 3 days prior to Day 1 they do not need to be repeated at Day 1
Haematology	X	X	X	X	X	X	X	X			
APTT and INR		As clinically indicated									
TSH, free T_3, and free T_4	X	X	X	X	X	X	X	X			Section 8.2.1 (core protocol)
Urinalysis		As clinically indicated									Section 8.2.1 (core protocol)
Pregnancy test	X		X		X	X	X	X			Section 8.2.1.2 (core protocol)
AE/SAE assessment	X	X	X	X	X	X	X	X	X		Section 8.3 (core protocol)
Study drug administration[c]											
Durvalumab	X		X		X	X	X				Section 6.2.1
Olaparib	X		X		X	X	X				Section 6.2.2
Drug accountability	X	X	X	X	X	X	X	X			Section 6.2.5

	C1 28 days Weeks 1-4		**C2** 28 days Weeks 5-8		**C3** 28 days Weeks 9-12	**C4** 28 days Weeks 13-16	**C5 – etc** All cycles 28 days	**Study drug disc.** (28 days after study drug disc.)	**Safety follow-up** (90 days after study drug disc.)	**Survival follow up**	**Notes**
Week	**1**	**3**	**5**	**7**	**9**	**13**	**17, 21, 25, 29 etc**				
Cycle day	**1**	**15**	**1**	**15**	**1**	**1**	**1**				
Window (days)	**0**[a]	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±7**	**±7**	**±7**	
Other assessments											
Blood for ctDNA assessments	X	X	X	X	X	X	X	X			Section 8.8 (core protocol)
Circulating soluble factors (plasma)	X	X	X			X		X			Section 8.8 (core protocol)
Whole blood for gene expression (PAXgene® RNA tubes)	X	X	X			X		X			Section 8.8 (core protocol)
PBMCs for flow cytometry (activation by PD-1 / CD8+)	X	X	X			X					Section 8.8 (core protocol)
TCR immuno-sequencing	X	X	X			X					Section 8.8 (core protocol)
Blood sample for ADA for durvalumab (pre-dose except at safety follow up)	X		X				X (C5D1) then Q12W in first year, then Q24W in second year		X		Section 8.5.3 (core protocol)
Tumour evaluation (CT or MRI) (RECIST 1.1)		Every 6 weeks ±1 week for the first 24 weeks relative to the date of first dose (Cycle 1 Day 1), then every 8 weeks ± 1 week thereafter, until objective disease progression as defined by RECIST 1.1 and confirmed with a subsequent scan (in the absence of clinically significant deterioration)									Section 8.1 (core protocol)
Biopsy on-treatment (mandatory)				X							Section 8.8 (core protocol). This should align with the first RECIST assessment.

	C1 28 days Weeks 1-4		**C2** 28 days Weeks 5-8		**C3** 28 days Weeks 9-12	**C4** 28 days Weeks 13-16	**C5 – etc** All cycles 28 days	**Study drug disc.** (28 days after study drug disc.)	**Safety follow-up** (90 days after study drug disc.)	**Survival follow up**	**Notes**
Week	**1**	**3**	**5**	**7**	**9**	**13**	**17, 21, 25, 29 etc**				
Cycle day	**1**	**15**	**1**	**15**	**1**	**1**	**1**				
Window (days)	**0**[a]	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±7**	**±7**	**±7**	
Biopsy on disease progression (mandatory only for re-allocated patients)								X			Section 8.8 (core protocol)
Subsequent cancer therapy									X	X	Section 8.1.3.1 (core protocol). Every 3 months
Survival status										X[b]	Section 8.1.3.1 (core protocol). Every 3 months

[a] Every effort should be made to minimise the time between allocation to treatment and starting treatment. Note, if main screening assessments have been performed within 3 days prior to C1D1, then assessments do not need to be performed on C1D1 pre-dose.

[b] Ad hoc collection of survival status may be requested for overall survival analyses.

[c] Following the final data cut-off for the module CSR (see Section 9.4.2 of the core protocol), any patients on study treatment may continue on treatment and should be assessed for safety according to standard local clinical practice. Study drug administration, SAE reporting and related safety assessment data should be recorded in the eCRF until 90 days after study drug discontinuation, when the patient will end participation in the study. The other assessments for the study will no longer be performed and those data will no longer be collected; the tumour evaluations will be performed as per standard of care. The survival follow-up will no longer be conducted.

ADA Anti-drug antibodies; AE adverse event; APTT activated partial thromboplastin time; C cycle; CD8+ cytotoxic T cell; CSR clinical study report; CT computed tomography; ctDNA circulating tumour DNA; D day; ECG electrocardiogram; eCRF electronic Case Report Form; INR international normalised ratio; RECIST 1.1 Response Evaluation Criteria in Solid Tumours 1.1; MRI magnetic resonance imaging; PBMC peripheral blood mononuclear cell; PD-1 programmed cell death-1; Q12W every 12 weeks; Q24W every 24 weeks; SAE serious adverse event; TCR T-cell receptor repertoire; TSH thyroid-stimulating hormone; T_3 triiodothyronine; T_4 thyroxine.

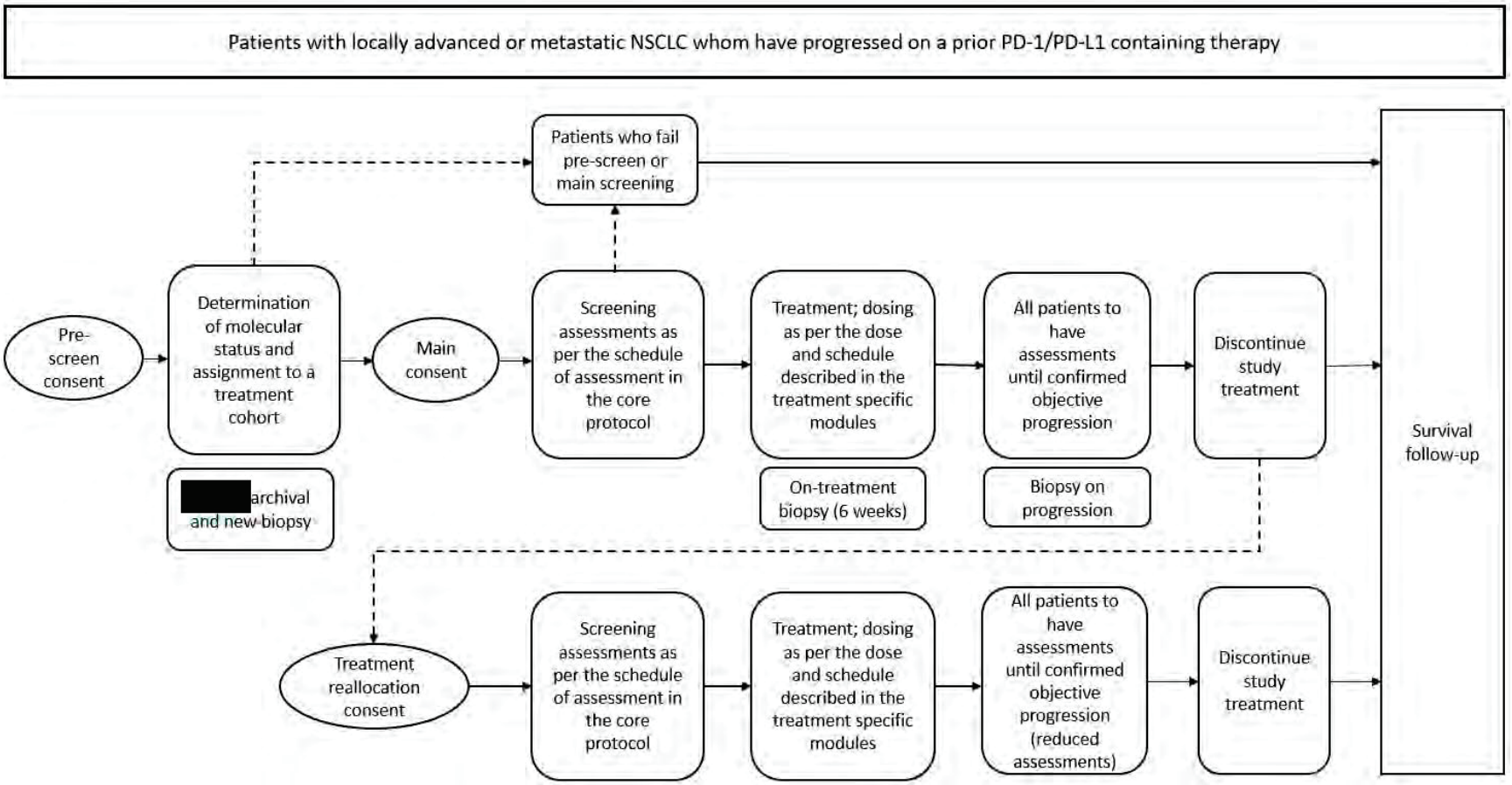
1.2 Synopsis

Please refer to Section 1.2 of the core protocol.

1.3 Schema

The general study design is summarised in Figure 1.

Figure 1 Study design



Note, from implementation of protocol v10.0, survival follow-up of screen failures and optional treatment re-allocation to a second treatment is no longer applicable.
ctDNA circulating tumour DNA; NSCLC non-small cell lung cancer; PD-1 programmed cell death-1; PD-L1 programmed cell death ligand 1.

2. INTRODUCTION

Study D6185C00001 (HUDSON) is a Phase II, open-label, multi-centre umbrella study in patients who have received an anti-programmed cell death-1 (PD-1)/anti-programmed cell death-ligand 1 (PD-L1) containing therapy and a platinum-doublet regimen for locally advanced or metastatic non-small cell lung cancer (NSCLC) either separately or in combination. The patient must have had disease progression on a prior line of anti-PD-1/PD-L1 therapy. The modular design allows the evaluation of the efficacy, safety, and tolerability of multiple study drugs. This module to the core study protocol describes Module 1, which will investigate the efficacy, safety, and tolerability of durvalumab administered in combination with olaparib.

2.1 Study rationale

As described in Section 2.2 of the core protocol, immune checkpoint inhibitors targeting the PD-1/PD-L1 pathway have shown significant activity in the first- and second-line treatment settings in patients with NSCLC. However, it is becoming evident that there is a new and significant patient population emerging that does not respond to anti-PD-1/PD-L1 containing therapy (primary resistance) or progresses during anti-PD-1/PD-L1 containing therapy (acquired resistance). There is currently no established therapy for patients who have developed resistance to PD-1/PD-L1 and platinum-doublet therapies, and novel treatments for these patients are urgently needed.

The aim of this umbrella study (D6185C00001) is to investigate multiple study drugs for the treatment of NSCLC in molecularly matched and non-matched patient populations after failure of immune checkpoint inhibitors, to identify patient populations who may respond favourably to novel anti-tumour therapies.

2.2 Background

Durvalumab and olaparib are both currently in clinical development as anti-cancer therapies in a variety of malignancies.

Durvalumab as a weight-based regimen of 10 mg/kg every 2 weeks (Q2W) has been approved for use in the treatment of patients with urothelial carcinoma (UC). On 16 February 2018, durvalumab was approved in the US for the treatment of patients with unresectable Stage III NSCLC. On 21 September 2018, durvalumab was approved in the European Union (EU) for the treatment of locally advanced, unresectable NSCLC in adults whose tumours express PD-L1 on ≥1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy. As of 12 July 2019, durvalumab is approved in over 45 countries for NSCLC. On 27 March 2020, the Food and Drug Administration approved durvalumab in combination with etoposide and either carboplatin or cisplatin as first-line treatment of patients with extensive-stage small cell lung cancer.

The olaparib capsule formulation was registered for use in the European Union (EU) and United States (US) in December 2014 for ovarian cancer. The olaparib tablet formulation is registered for use in the US, EU and Japan for second-line ovarian cancer, germline breast cancer susceptibility gene mutated (*gBRCAm*) breast cancer and *BRCAm* first-line ovarian cancer. In China, the tablet formulation is registered for use as maintenance treatment following response to platinum-based chemotherapy in patients with PSR ovarian cancer and as first-line maintenance in *BRCAm* advanced ovarian cancer patients. Please refer to local Prescribing Information for approved indications.

Module 1 will investigate both agents in combination, to test the hypothesis that the combination will result in complementary anti-tumour activity. Brief background on durvalumab and olaparib, including their mechanisms of action, is provided below. For detailed descriptions of the chemistry, pharmacology, efficacy, and safety of durvalumab and olaparib, refer to the respective Investigator's Brochures.

The study will recruit both biomarker-matched and biomarker non-matched patients (see Section 4.1). The biomarkers of interest are aberrations in genes involved in homologous recombination repair (*HRRm*) and in liver kinase B1 (*LKB1*) (also known as *STK11;* serine threonine kinase 11, see Section 4.1).

2.2.1 Durvalumab

2.2.1.1 Overview of durvalumab

Expression of PD-L1 protein is an adaptive immune response that helps tumours evade detection and elimination by the immune system. PD-L1 can be induced by inflammatory signals (eg, interferon-gamma) and can be expressed on both tumour cells and tumour-associated immune cells in tumour microenvironment. PD-L1 blocks T-cell function and activation through interaction with PD-1 and CD80 (B7.1). By binding to its receptors, PD-L1 reduces cytotoxic T-cell activity, proliferation, and cytokine production. Durvalumab is a fully human, high affinity, immunoglobulin G1 kappa monoclonal antibody that selectively blocks the interaction of PD-L1 with PD-1 and cluster of differentiation (CD)80 (B7.1) while leaving PD-1/ programmed cell death ligand-2 interaction intact. Durvalumab does not induce antibody dependent cell-mediated cytotoxicity. Selective blockade of PD-L1/PD-1 and PD-L1/CD80 interactions enhances antitumour immune responses. These antitumour responses may result in tumour elimination.

Durvalumab is approved in a number of territories including the US, EU, Japan, Canada and Brazil under the brand name IMFINZI™ Injection.

The recommended dose as per the IMFINZI package insert is 10 mg/kg administered as an IV infusion over 60 minutes every 2 weeks (Q2W).

For more information, please refer to the latest version of the Durvalumab Investigator's Brochure.

2.2.1.2 Durvalumab data

To date, durvalumab has been given to more than 12000 patients as part of ongoing studies either as monotherapy or in combination with other anticancer agents. Details on the safety profile of durvalumab monotherapy are summarised below. Refer to the current durvalumab IB for a complete summary of pre-clinical and clinical information including safety, efficacy, and pharmacokinetics (PK).

Clinical activity in locally advanced NSCLC

The efficacy of durvalumab was evaluated in the PACIFIC Study, a randomised, double-blind, placebo-controlled, multicentre study in 713 patients with histologically or cytologically confirmed locally advanced, unresectable NSCLC. Patients had completed definitive platinum-based chemoradiation within 1 to 42 days prior to initiation of the study and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Ninety-three percent of patients had received a total dose of 54 to 66 Gy of radiation. The study excluded patients who had progressed following concurrent chemoradiation therapy, patients with active or prior documented autoimmune disease within 2 years of initiation of the study; a history of immunodeficiency; a history of severe immune-mediated adverse reactions; medical conditions that required systemic immunosuppression, except physiological dose of systemic corticosteroids; active tuberculosis or hepatitis B or C or HIV infection or patients receiving live attenuated vaccine within 30 days before or after the start of durvalumab. Patients were randomised 2:1 to receive 10 mg/kg durvalumab (n=476) or 10 mg/kg placebo (n=237) via IV infusion Q2W for up to 12 months or until unacceptable toxicity or confirmed disease progression. Randomisation was stratified by gender, age (<65 years vs. ≥65 years) and smoking status (smoker vs. nonsmoker). Patients with disease control at 12 months were given the option to be re-treated upon disease progression. Tumour assessments were conducted every 8 weeks for the first 12 months and then every 12 weeks thereafter.

The demographics and baseline disease characteristics were well balanced between study arms. Baseline demographics of the overall study population were as follows: male (70%), age ≥65 years (45%), White (69%), Asian (27%), other (4%), current smoker (16%), past-smoker (75%), and never smoker (9%), World Health Organisation (WHO)/ECOG PS 0 (49%), WHO/ECOG PS 1 (50%). Disease characteristics were as follows: Stage IIIA (54%), Stage IIIB (44%), histological subgroups of squamous (47%), non-squamous (53%), PD-L1 expression in tumour cells (TC) ≥ 25% (22%), PD-L1 expression TC<25% (41%). (PD-L1 status was retrospectively analysed using the Ventana PD-L1 [SP263] Assay in 451 patients with available samples, taken prior to concurrent chemoradiation therapy).

At the time of the interim progression-free survival (PFS) analysis, the median PFS by blinded independent central review (BICR) was significantly longer with durvalumab treatment (16.8 months) compared with placebo (5.6 months); hazard ratio 0.52; 98.9% CI: 0.39, 0.70; p<0.0001. At the time of the interim overall survival (OS) analysis, the median OS was not reached for the durvalumab arm and was 29.1 months for the placebo arm; hazard ratio, 0.69; 95% CI, 0.55, 0.86). The 36-month OS rate was 57.0% with durvalumab vs 43.5% with placebo.

Clinical activity in recurrent and metastatic NSCLC

Based on current data from the ongoing Study CD ON MEDI4736-1108 (NCT01693562), evidence of clinical activity with durvalumab has been observed. The following responses were observed in patients with NSCLC.

Overall, clinical activity was observed in both the PD-L1 high (defined as having tumour cells [TC] ≥25%) and PD-L1 low/negative (defined as TC <25%) subgroups, however, patients with PD-L1 high tumours had higher objective response rates (ORRs).

The ORR per BICR was 21.8% and 6.4% in patients with PD-L1 high and low/negative tumours, respectively, and 15.3% in the overall population regardless of PD-L1 expression. The ORR was 25.9%, 14.3% and 11.5% in the 1L, 2L and 3L+ cohorts, respectively. Median duration of response (DOR) was 17.74 months. Median OS was 12.4 months; median OS was 21.0, 11.8 and 9.3 months in the 1L, 2L and 3L+ cohorts, respectively. The OS rate at 24 months was 29.6%.

The ATLANTIC study in third-line or higher NSCLC showed higher ORR and survival outcomes in high PD-L1 positive patients. Across cohorts the ORR ranged from 3 to 43%, median PFS ranged from 1.8 to 5.5 months and median OS ranged from 5.9 to 13.6 months but was not reached at the time of initial reporting in the >90% PD-L1 expressors. The ORR and survival outcomes reported in durvalumab studies are in keeping with other similar agents targeting the PD-1/PD-L1 axis (Garassino et al 2017).

Preliminary efficacy data from the MYSTIC study in first-line advanced or metastatic NSCLC showed that in PD-L1 high (≥ 25% TC) NSCLC, median PFS by BICR was 4.7 months for durvalumab monotherapy and 5.4 months for chemotherapy; hazard ratio of 0.87; 99.5% CI: 0.593, 1.285; p=0.324. The median OS was 16.3 months for the durvalumab arm and 12.9 months for the chemotherapy arm; hazard ratio for death was 0.76; 97.54% CI: 0.564, 1.019; p=0.036. The 24-month OS rate was 38.3% versus 22.7% and the 12-month PFS rate was 32.3% vs 14.3% for the durvalumab and chemotherapy arms respectively. When durvalumab was administered in combination with tremelimumab, the median PFS by BICR was 3.9 months for durvalumab + tremelimumab and 5.4 months for chemotherapy; hazard ratio of 1.05; 99.5% CI: 0.722, 1.534; p=0.705. The median OS was 11.9 months for the durvalumab

+ tremelimumab arm and 12.9 months for the chemotherapy arm; hazard ratio for death was 0.85; 98.77% CI: 0.611, 1.173; p=0.202. The 24-month OS rate was 35.4% versus 22.7% and the 12-month PFS rate was 25.8% versus 14.3% for the durvalumab + tremelimumab and chemotherapy arms respectively.

Immuno-oncology agents targeting the PD-1/PD-L1 pathway have demonstrated activity as monotherapy and in combination with chemotherapy in patients who are immunotherapy-naïve. However, the present study will recruit patients who either have primary resistance to anti-PD-1/PD-L1 therapy or who developed acquired resistance while on anti-PD-1/PD-L1 therapy. Thus, in this immunotherapy-resistant setting, durvalumab will be administered in combination with an agent that has a different and complementary mechanism of action in order to maximise the likelihood of clinical activity.

2.2.2 Olaparib

2.2.2.1 Overview of olaparib

The approved tradename for olaparib is LYNPARZA™. On 27 July 2017, AstraZeneca and Merck & Co., Inc., (Merck; known as MSD outside of the US and Canada) announced a global strategic oncology collaboration to co-develop and co-commercialise olaparib for multiple cancer types. The companies currently develop olaparib jointly, both as monotherapy and in combination with other potential medicines.

The majority of the early phase studies were performed with the capsule formulation of olaparib. Since 2012/2013 most new studies, including the Phase III registration studies, are being performed with the tablet formulation which was designed to deliver the therapeutic dose of olaparib in fewer dose units than the capsule.

The capsule formulation of olaparib was registered for use in the EU and US in December 2014, and has been approved in 25 other markets globally.

The tablet formulation has subsequently been registered in the US in August 2017, in Japan in January 2018, in the EU in May 2018 and in China in August 2018.

For more information, please refer to the latest version of the olaparib Investigator's Brochure.

2.2.2.2 Olaparib data

Up to and including 15 December 2019 approximately 13555 patients are estimated to have received olaparib in the clinical programme (including AstraZeneca-sponsored studies and AstraZeneca-Merck Alliance sponsored studies [7638 patients], Investigator Sponsored Studies (ISS) and collaborative group studies [5061 patients] and a Managed Access Programme [MAP; 856 patients]). An estimated 8494 patients with ovarian, breast, pancreatic, gastric, prostate and a variety of other solid tumours are estimated to have received treatment with olaparib in AstraZeneca-sponsored, interventional studies and AstraZeneca-Merck

Alliance sponsored studies (7638 patients) and the MAP (856 patients). Since 2013, most new clinical studies have utilised the tablet formulation which was designed to deliver the therapeutic dose of olaparib in fewer dose units than the capsule. Of the 7638 patients, 1578 received the capsule formulation, 6035 received the tablet formulation and 25 received both capsule and tablet. In these studies, olaparib was given either as monotherapy (5135 patients) or in combination with chemotherapy or other anti-cancer agents (eg, capecitabine, vinorelbine, eribulin, abiraterone, topotecan, gemcitabine, carboplatin and paclitaxel, paclitaxel or liposomal doxorubicin), including studies where patients received monotherapy and combination therapy sequentially (2503 patients). Approximately 2674 patients have received comparator or placebo across the olaparib development programme in AstraZeneca-sponsored studies and AstraZeneca-Merck Alliance sponsored studies.

Post-marketing patient exposure is estimated to be 13655 patient years for olaparib capsules and 16179 patient years for olaparib tablets up to 30 November 2019.

Inhibition of PARP in sensitive tumour cells, for example those carrying mutations in the *BRCA1* or *BRCA2* genes, results in accumulating levels of DNA damage and genomic instability, ultimately resulting in cell death (Farmer et al 2005). Accumulating DNA damage has the potential to modify the immunogenicity of tumours through a number of key mechanisms:

- Triggering of intracellular signalling events that result in the activation of nuclear factor kappa B (NFκB) and interferon regulatory factor 7 (IRF7). These transcriptional regulators result in the increased production of cytokines and chemokines that have the potential to promote anti-tumor immunity, such as Type I IFNs (Chatzinikolaou et al 2014).
- Upregulation of surface receptors such as major histocompatibility complex (MHC), ligands for natural-killer group 2, member D (NKG2D) and inducible T-cell costimulatory ligand (ICOSL), which render tumour cells more visible to detection by cytotoxic T-cells (Tang et al 2014).
- Death of tumour cells and release of antigen, which may help to promote antigen presentation and immune priming (Kroemer et al 2013).

Based on this basic biology, the hypothesis to be tested in this study is that increased DNA damage triggered through PARP inhibition will result in enhanced anti-tumor immunity that can be further enhanced through combination with an immune checkpoint inhibitor in advanced cancers. This hypothesis is supported by published studies in mouse models of cancer, demonstrating that administration of a PARP inhibitor to sensitive tumour types results in increased T-cell infiltration and activation within tumours (Higuchi et al 2015; Huang et al 2015). There is also evidence that patients with prostate cancer with aberrations to the ataxia telangiectasia mutated *(ATM)*-gene responded well to olaparib treatment (Mateo et al 2015).

In agreement with this hypothesis, olaparib was associated with a statistically significant improvement in PFS as a maintenance treatment in ovarian cancer (Chatzinikolaou et al 2014), and recent analysis suggests this may translate into a survival advantage (Ledermann et al 2014). These effects would be expected to help promote an effective anti-tumour immune response. In keeping with this hypothesis, several tumour types with genetic defects expected to lead to increased DNA damage show evidence of enhanced immune recognition. For example, *BRCAm* tumour cells are associated with higher levels of tumour infiltrating lymphocytes and secreting lymphocyte attractants (eg, C-X-C motif ligand [CXCL]-10) and immune suppressive ligands such as PD-L1 (Mulligan et al 2014).

There are ongoing studies with olaparib in different tumour types including NSCLC. Monotherapy is being explored in randomised placebo-controlled investigator lead trials, PIN (NCT01788332) and PipSEN (NCT02679963) in the UK and France. There is a third study at the NCI of olaparib in combination with durvalumab in a NSCLC cohort at the same doses of both agents as in the HUDSON study (NCT02484404). No safety concerns have been raised in any of these studies.

Olaparib is currently being studied in multiple Phase III studies, including in ovarian cancer, breast cancer, pancreatic cancer, and prostate cancer as monotherapy and in combination with other treatments. Data from the development programme indicate that olaparib is generally well tolerated at monotherapy doses up to 400 mg bd (capsule formulation) and 300 mg bd (tablet formulation) in patients with solid tumours. Administration of olaparib monotherapy has been associated with adverse reactions generally of mild or moderate severity (CTCAE Grade 1 or 2) and generally not requiring treatment discontinuation. Published data link DNA repair gene mutation frequency, tumour mutational burden, and clinical benefit from checkpoint inhibition in NSCLC (Rizvi et al 2015). This study will directly test the clinical hypothesis that inhibiting DNA repair can improve lung tumour immunogenicity.

2.3 Benefit/risk assessment

2.3.1 Olaparib in combination benefit/risk

Data from Phase I dose escalation studies of olaparib in combination with various chemotherapy agents indicated an increase in bone marrow toxicity (anaemia, neutropenia, thrombocytopenia) greater than expected if the agents had been administered alone. However, tolerable regimens combining olaparib with paclitaxel, attenuated dosed liposomal doxorubicin and attenuated dosed carboplatin/paclitaxel have been established, supporting studies in the combination setting.

Administration of olaparib in combination with DTIC, topotecan, gemcitabine, cisplatin, paclitaxel or carboplatin + paclitaxel resulted in a lower maximum tolerated dose (MTD) of olaparib compared with its administration as a monotherapy.

Administration of olaparib with abiraterone in patients with metastatic castration-resistant prostate cancer (mCRPC) resulted in a numerical imbalance of cardiovascular events between the treatment arms in Part B, with a greater number of patients in the olaparib + abiraterone arm experiencing such events, most notably those of greater severity. The clinical significance of this is unclear and the interpretation is limited by the small sample size of the safety analysis set, some imbalances in relevant baseline characteristics, lack of confirmation of cardiac failure diagnoses and lack of biological plausibility that olaparib would contribute to, and increase, the cardiovascular risk over that known for abiraterone monotherapy.

Toxicities considered to be associated with administration of olaparib include haematological effects (anaemia, neutropenia, lymphopenia, leukopenia, thrombocytopenia, mean corpuscular volume [MCV] elevation), decreased appetite, nausea and vomiting, diarrhoea, dyspepsia, stomatitis, upper abdominal pain, dysgeusia, fatigue (including asthenia), increase in blood creatinine, headache, dizziness, hypersensitivity, rash, dermatitis, cough and dyspnoea.

The dose of olaparib for this study was selected based on the results of 2 studies:

- Study ESR-14-10366 (independent NCI study, NCT02484404), which is an ongoing Phase I study of olaparib in combination with durvalumab in patients with solid tumours.
- Study D081KC00001 (MEDIOLA, NCT02734004), which is an ongoing Phase I/II study of olaparib in combination with durvalumab in patients with advanced solid tumours.

Based on the data available from these studies, the dose of olaparib to be used in this study will be the recommended monotherapy dose of 300 mg twice daily (BD) (tablet formulation) (see Section 4.3.2).

Cases of pneumonitis, myelodysplastic syndrome (MDS)/acute myeloid leukaemia (AML) and new primary malignancies have been reported. Evidence from across the development programme for olaparib does not support a conclusion that there is a causal relationship between olaparib and these events. These are important potential risks for olaparib and are being kept under close pharmacosurveillance.

2.3.2 Durvalumab and olaparib in combination

A combination of an immune-mediated therapy, such as durvalumab with a targeted therapy has the potential to increase anti-tumour activity. The immune system can identify and eliminate cancerous cells, but anti-tumour immune response is often held in check by immunosuppressive mechanisms, which can be beneficially altered by the action of olaparib. One such suppressive mechanism is expression of PD-L1 on the surface of tumour and immune cells.

Encouraging clinical activity, combined with acceptable and manageable safety, has been seen to date with durvalumab in combination therapy studies. In general, the toxicity profiles of

durvalumab and of olaparib are non-overlapping. Pneumonitis is the most important potential exception. The management guidelines for pneumonitis (see Section 8.4.5) integrate the guidance provided for these 2 agents.

Monoclonal antibodies are not metabolised through classical hepatic enzyme pathways. Olaparib has previously been combined with another monoclonal antibody (bevacizumab) without significant drug-drug interaction. Therefore, no pharmacokinetic (PK) interaction is anticipated within this study.

As described in Section 2.3 of the core protocol, patients recruited to this study are not expected to have other treatment options apart from monotherapy chemotherapy, such as docetaxel. The survival outcome and toxicity profile of chemotherapy in this setting mean that other active therapies are highly desirable and present a potential advantage for patients.

The study design aims to identify patient populations who may respond favourably to novel anti-tumour therapies. Based upon the available non-clinical and clinical safety data, the limited survival benefit provided by the currently available treatment options to patients, the limited life expectancy due to malignant disease, and the hypothesis of the complementary effect of the 2 agents, the investigation of the potential therapeutic efficacy of the combination of durvalumab with olaparib in patients with advanced or metastatic NSCLC is acceptable, and the overall benefit/risk assessment supports the proposed study design. A proposed benefit to seeking signals by this biomarker stratification strategy includes the opportunity to discover potential increased sensitivity to olaparib in patients with NSCLC bearing additional mutations vis-à-vis those bearing only the *BRCA* mutations validated in other indications such as ovarian or breast cancer.

3. OBJECTIVES AND ENDPOINTS

Please refer to the core protocol.

4. STUDY DESIGN

4.1 Overall design

This is an open-label, multi-centre, umbrella study in patients who have received an anti-PD-1/PD-L1 containing therapy and a platinum-doublet regimen for locally advanced or metastatic NSCLC either separately or in combination. The patient must have had disease progression on a prior line of anti-PD-1/PD-L1 therapy. For an overview of the study design see Figure 1; further details on the overall design are provided in Section 4 of the core protocol. For details on the study drugs given in Module 1, see Section 6.1 of this module.

Module 1 will evaluate the efficacy, safety, and tolerability of durvalumab (given intravenously [IV]) in combination with olaparib (given orally) in the 4 cohorts of patients: biomarker-matched and biomarker non-matched, as follows:

- Cohorts A.1 will investigate the safety, tolerability, and anti-tumour activity of durvalumab given IV at 1500 mg every 4 weeks (Q4W) ±2 days in combination with olaparib given orally at 300 mg BD:
  - Cohort A.1.HRR for patients whose tumours have detectable aberrations in *HRRm*
  - Cohort A.1.LKB for patients with detectable aberrations in *LKB1*
- Cohorts B.1 will investigate the safety, tolerability, and anti-tumour activity of durvalumab given IV at 1500 mg Q4W ±2 days in combination with olaparib given orally at 300 mg BD, stratified by prior response to immunotherapy; primary resistance (Cohort B.1.PRI), or acquired resistance (Cohort B.1.ACQ). These terms are defined as follows:
  - Primary resistance; patients who had anti-PD-1/PD-L1 containing therapy but had progression of disease (PD) within ≤24 weeks from the start of treatment.
  - Acquired resistance; patients who had progressive disease >24 weeks from the start of anti-PD-1/PD-L1 containing therapy whilst still on that treatment.

A study flow diagram is provided in the core protocol (Figure 4).

4.2 Scientific rationale for study design

The study aims to identify patient populations who may respond favourably to novel anti-tumour therapies, and the modular design allows evaluation of the efficacy, safety, and tolerability of multiple study drugs. The study requires an open-label design owing to the different schedules and routes of administration of the study drugs.

The scientific background for inclusion of biomarker-matched and biomarker non-matched cohorts is as follows.

Thousands of DNA damaging events occur daily in cells due to external insults and endogenous biochemistry. This damage leads to nucleotide modification, single strand DNA breaks (SSBs) and double strand DNA breaks (DSBs). These are detected and resolved by the integrated action of cell cycle checkpoints and DNA repair pathways to ensure genomic stability (O'Connor 2015).

If the level of DNA damage exceeds the capacity to repair, cells will trigger cell death through apoptosis. Cells are particularly sensitive to the level of DSBs, the most genotoxic form of DNA damage, due to the consequences DSBs have for accurate chromosome segregation during cell division. Double strand DNA breaks are repaired through the *HRR* pathway (O'Connor 2015).

PARP is a key enzyme in the repair of SSBs, the most common form of DNA damage. Olaparib is a PARP inhibitor that blocks this repair activity and traps PARP on the single strand DNA, leading to DSBs, and dependence on the *HRR* capacity to maintain genomic stability and cell survival (Pommier et al 2016).

Cohort A.1.HRR (biomarker-matched: HRRm): In tumour cells with *HRR*-deficiency, the capacity for DSB repair is reduced so DSBs accumulate leading to selective tumour cell death through apoptosis (Pommier et al 2016). The death of *HRR*-deficient tumour cells is expected to release tumour antigens and cause changes to the tumour microenvironment that promote antigen presentation, priming the immune response (Kroemer et al 2013). Immune checkpoint blockade by durvalumab at the same time is expected to overcome the inhibitory action of PD-L1 on T-cell activation.

Cohort A.1.LKB (biomarker-matched: LKB1 mutant): In non-clinical models, *LKB1* loss leads to accumulation of neutrophils with T-cell–suppressive effects, along with a corresponding increase in the expression of T-cell exhaustion markers, tumour-promoting cytokines and a reduction in tumour-infiltrating lymphocytes (Koyama et al 2016). Consistent with this, patients with *LKB1*-mutant NSCLC have high levels of primary resistance to immunotherapy (Skoulidis et al 2017). Liver kinase B1 is activated by *ATM* during DSB repair, and the reduced DNA repair capability of *LKB1*-mutant cells makes them sensitive to PARP inhibition leading to selective tumour cell death (Wang et al 2016). The death of *LKB1* tumour cells is expected to release tumour antigens and cause changes in the tumour microenvironment that reverse their resistance to immunotherapy. Checkpoint blockade by durvalumab at the same time is expected to overcome the inhibitory action of PD-L1 ligand on T-cell activation.

Cohorts B.1.PRI and B.1.ACQ (biomarker non-matched: primary resistance; acquired resistance): the proliferative drive and genomic instability of cancer cells leads to high background levels of DNA damage and repair. Increasing these levels of DNA damage by PARP inhibition leads to a high volume of DNA repair and the accumulation of unincorporated DNA fragments in the cytosol, activating the stimulator of IFN genes (STING)/TANK-binding kinase-1 (TBK1)/IRF3 innate immune response, which is expected to reverse resistance to immunotherapy (Parkes et al 2016). Checkpoint blockade at the same time by durvalumab is expected to overcome the inhibitory action of PD-L1 on T-cell activation.

4.3 Justification for dose

4.3.1 Justification for durvalumab dose

A durvalumab dose of 20 mg/kg Q4W is supported by in vitro data, pre-clinical activity, clinical PK/pharmacodynamics, biomarkers, and activity data from Study CD-ON-MEDI4736-1108 (hereafter referred to as Study 1108) in patients with advanced solid tumors

and from a Phase I study performed in Japanese patients with advanced solid tumor (D4190C00002).

PK/Pharmacodynamic data

Based on available PK/pharmacodynamic data from ongoing Study 1108 with doses ranging from 0.1 to 10 mg/kg Q4W or 15 mg/kg Q4W, durvalumab exhibited non-linear (dose dependent) PK consistent with target-mediated drug disposition. The PK approached linearity at ≥3 mg/kg Q4W, suggesting near complete target saturation (membrane-bound and sPD-L1), and further shows that the durvalumab dosing frequency can be adapted to a particular regimen given the linearity seen at doses higher than 3 mg/kg. The expected half-life with doses ≥3 mg/kg Q4W is approximately 21 days. A dose-dependent suppression in peripheral sPD-L1 was observed over the dose range studied, consistent with engagement of durvalumab with PD-L1. A low level of immunogenicity has been observed. No patients have experienced immune-complex disease following exposure to durvalumab. (For further information on immunogenicity, please see the current durvalumab IB.)

A population PK model was developed using the data from Study 1108 (doses=0.1 to 10 mg/kg Q2W or 15 mg/kg Q4W; Fairman et al 2014). Multiple simulations indicate that a similar overall exposure is expected following both 10 mg/kg Q4W and 20 mg/kg Q4W regimens, as represented by AUC_{ss} (4 weeks). Median $C_{max,ss}$ is expected to be higher with 20 mg/kg Q4W (~1.5-fold) and median $C_{trough,ss}$ is expected to be higher with 10 mg/kg Q4W (~1.25-fold). Clinical activity with the 20 mg/kg Q4W dosing regimen is anticipated to be consistent with 10 mg/kg Q4W with the proposed similar dose of 20 mg/kg Q4W expected to (a) achieve complete target saturation in majority of patients; (b) account for anticipated variability in PK, pharmacodynamics, and clinical activity in diverse cancer populations; (c) maintain sufficient PK exposure in case of ADA impact; and (d) achieve PK exposure that yielded maximal antitumor activity in animal models.

Given the similar area under the serum drug concentration-time curve (AUC) and modest differences in median peak and trough levels at steady state, the observation that both regimens maintain complete sPD-L1 suppression at trough, and the available clinical data, the 20 mg/kg Q4W and 10 mg/kg Q4W regimens are expected to have similar efficacy and safety profiles, supporting further development with a dose of 20 mg/kg Q4W.

Clinical data

Refer to the current durvalumab IB for a complete summary of clinical information including safety, efficacy, and PK at the 20 mg/kg Q4W regimen.

Rationale for fixed dosing

A population PK model was developed for durvalumab using monotherapy data Study 1108 (N=292; doses = 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W; solid tumors). Population PK

analysis indicated only minor impact of body weight on the PK of durvalumab (coefficient of ≤0.5). The impact of body weight-based (10 mg/kg Q2W) and fixed dosing (750 mg Q2W) of durvalumab was evaluated by comparing predicted steady state PK concentrations (5th, median, and 95th percentiles) using the population PK model. A fixed dose of 750 mg was selected to approximate 10 mg/kg (based on median body weight of ~75 kg). A total of 1000 patients were simulated using body weight distribution of 40 to 120 kg. Simulation results demonstrate that body weight-based and fixed dosing regimens yield similar median steady state PK concentrations with slightly less overall between-patient variability with fixed dosing regimen.

Similar findings have been reported by others (Narwal et al 2013, Ng et al 2006, Wang et al 2009, Zhang et al 2012). Wang and colleagues investigated 12 monoclonal antibodies and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies (Wang et al 2009). In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-patient variability in PK/pharmacodynamic parameters (Zhang et al 2012).

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar PK exposure and variability, AstraZeneca considered it feasible to switch to fixed dosing regimens. Based on average body weight of 75 kg, a fixed dose of 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) is included in the current study.

An exception to 1500 mg fixed dosing is made for patients with low body weight (below 30 kg). Patients with a body weight of 30 kg or less must receive weight-based dosing, equivalent to 20 mg/kg, until weight increases to greater than 30 kg. At this time, fixed dosing data for patients weighing below 30 kg (corresponding to doses greater than 50 mg/kg) are not available and are not yet supported by product development.

Thus, the clinical activity observed coupled with the safety profile, translational science correlates, and non-clinical data supports further development with a dose of 1500 mg Q4W. The dose of durvalumab will not be modified during the study.

4.3.2 Justification for olaparib dose

The recommended olaparib monotherapy tablet dose is 300 mg BD (Mateo et al 2016), and this is also the planned dose for this study having been confirmed as safe and tolerable in combination with durvalumab in an independent Phase I study in patients with solid tumours (the NCI Study ESR-14-10366 (NCT02484404)).

The NCI Study ESR-14-10366 is an ongoing Phase I study of olaparib in combination with durvalumab in patients with solid tumours (Lee et al 2017). Durvalumab was administered at 10 mg/kg Q2W or 1500 mg Q4W with olaparib tablets BD on 2 schedules. The primary

endpoint was the recommended Phase II dose (RP2D). Response rate and PK analysis were secondary end points. Between June 2015 and May 2016, 26 women were enrolled. The RP2D was durvalumab 1500 mg Q4W with olaparib 300 mg BD. No dose-limiting toxicity was recorded with durvalumab plus olaparib. Two PRs (≥15 months and ≥11 months) and 8 stable diseases ≥4 months (median, 8 months [4 to 14.5 months]) were seen in patients who received durvalumab plus olaparib, yielding an 83% disease control rate. Response to therapy was independent of PD-L1 expression. To our knowledge, this is the first reported anti-PD-L1 plus olaparib combination therapy. The RP2D of durvalumab plus olaparib is tolerable and active. Phase II studies with biomarker evaluation are ongoing.

Considering emerging PK data from ongoing studies, there is there is no evidence to indicate any ethnic sensitivity in Asian patients compared to Western patients.

Olaparib at a dose of 300 mg BD in combination with durvalumab is also currently being investigated in the ongoing Study D081KC00001 in patients with advanced solid tumours (now fully enrolled), in Study D081RC00001 in patients with newly diagnosed advanced ovarian cancer, in Study D993IC00003 in patients with unresectable Stage IV urothelial cancer, in Study D9102C00001 in patients with NSCLC.

Based on these data, the tablet dose of olaparib to be used in this study will be the recommended monotherapy tablet dose, which has been established at olaparib 300 mg BD.

4.3.2.1 Olaparib dose in patients with renal impairment

Patients with mild and moderate renal impairment can be given olaparib. The influence of mild and moderate renal impairment on the PK of olaparib has been evaluated in Study D0816C00006 (NCT01894256). D0816C00006 was a 2-part study in patients with advanced solid tumours: Part A assessed the effect of mild or moderate renal impairment on the PK of olaparib in patients with advanced solid tumours following a single oral 300 mg tablet dose of olaparib; Part B allowed patients continued access to olaparib (300 mg BD) after the PK phase was completed.

After a single oral administration of the tablet formulation (300 mg) to patients with moderate renal impairment, geometric least squares mean, area under the curve (G_{LSmean} AUC) increased by 44% (mean ratio 1.44; 90% CI: 1.10, 1.89) compared with patients with normal renal function and G_{LSmean} maximum plasma concentration (C_{max}) was also increased by 26% (mean ratio 1.26; 90% CI:1.06, 1.48). The percentage of the dose eliminated (Fe %) in urine as unchanged drug was half that observed for patients with normal renal function (8% compared with 16% for patients with normal renal function). An olaparib dose reduction to 200 mg BD is recommended for patients with moderate renal impairment.

4.4 End of study definition

Please refer to the core protocol.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

Each patient should meet all the inclusion criteria and none of the exclusion criteria for this study in order to be assigned to a study cohort. Under no circumstances can there be exceptions to this rule. Patients who do not meet the entry requirements are screen failures; refer to Section 5.4 of the core protocol.

5.1 Inclusion criteria (Module 1-specific)

Patients are eligible to be included in the study only if all the following inclusion criteria apply. Please also refer to Section 5.1 of the core protocol for the inclusion criteria applicable to all modules in the study. Additional inclusion criteria applicable to Module 1 only are described in this section.

I-1 Patients must fulfil all the core eligibility criteria.

I-2 Haemoglobin (Hb) ≥10 g/dL and no blood transfusions within 28 days.

I-3 Identification of molecular aberrations:

- Cohort A.1.HRR: deleterious mutations, deletions or truncations in any one of a panel of *HRR* genes
- Cohort A.1.LKB: deleterious mutations, deletions or truncations in *LKB1* gene

5.2 Exclusion criteria (Module 1-specific)

Patients must not enter Module 1 of the study if any of the following exclusion criteria apply. Please also refer to Section 5.2 of the core protocol for the exclusion criteria applicable to all modules in the study. Additional exclusion criteria applicable to Module 1 only are described in this section.

I-1 Patients meet any of the core exclusion criteria.

I-2 Creatinine clearance ≤50 mL/min as calculated by Cockcroft-Gault equation (see Table 5 in the core protocol for the calculation).

I-3 Concomitant use of known strong cytochrome P450 (CYP3A) inhibitors (eg, itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (eg, ciprofloxacin, erythromycin, diltiazem, fluconazole,

verapamil). The required washout period prior to starting study treatment is 2 weeks. Dihydropyridine calcium-channel blockers are permitted for management of hypertension. Please also see Section 6.5.

I-4 Concomitant use of known strong (eg, phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) or moderate CYP3A inducers (eg, bosentan, efavirenz, modafinil). The required washout period prior to starting study treatment is 5 weeks for enzalutamide or phenobarbital and 3 weeks for other agents. Please also see Section 6.5.

I-5 Previous treatment with a PARP inhibitor, including olaparib.

I-6 Patients with (or with previous history of) MDS or AML and patients with pre-dose features suggestive of MDS or AML on peripheral blood smear or bone marrow biopsy. Note that a bone marrow biopsy, in the absence of a clinical indication, is not necessary for study entry.

I-7 Whole blood transfusions in the last 120 days prior to entry to the study (packed red blood cells and platelet transfusions are acceptable, as long as not received within 28 days of start of treatment).

I-8 Inability to swallow the formulated product.

For procedures for withdrawal of incorrectly enrolled patients see Section 7.3 of the core protocol.

5.3 Lifestyle restrictions

5.3.1 Restrictions applicable to durvalumab

Patients should not donate blood or blood components while participating in this study and through 90 days after receipt of the final dose of durvalumab or until alternate anticancer therapy is started.

Immunosuppressive medications including, but not limited to systemic corticosteroids at doses beyond 10 mg/day of prednisone or equivalent, methotrexate, azathioprine and tumour necrosis factor alpha blockers are prohibited. Use of immunosuppressive medications for the management of study drug-related AEs and in patients with contrast allergies is acceptable. In addition, use of topical, inhaled and intranasal corticosteroids is permitted (see Table 3).

Live attenuated vaccines within 30 days of durvalumab dosing are prohibited (ie, 30 days prior to the first dose, during treatment with durvalumab and for 180 days post-discontinuation of durvalumab) (see Table 3). Inactivated viruses, such as those in the influenza vaccine or authorised and approved Coronavirus Disease 2019 (COVID-19) vaccines, are permitted (see Table 4).

5.3.2 Restrictions applicable to olaparib

Patients should avoid concomitant use of drugs, herbal supplements and/or ingestion of foods known to modulate CYP3A4 enzyme activity from the time they enter the screening period until 30 days after the last dose of study medication. It is recommended to avoid consumption of grapefruit juice while taking olaparib. Full details of treatment restrictions for patients receiving olaparib are provided in Section 6.5.

Reproduction

Please refer to section 5.3 of the core protocol.

5.4 Screen failures

Please refer to Section 5.4 of the core protocol.

6. STUDY TREATMENTS

Study treatment is defined as any study drug(s) (including marketed product comparator and placebo) or medical device(s) intended to be administered to a study participant according to the study protocol. Study treatment in Module 1 refers to durvalumab and olaparib.

6.1 Treatments administered

6.1.1 Study drugs

Table 2 Study drugs

Study drug name:	Olaparib	Durvalumab
Dosage formulation:	Film-coated 150 mg and 100 mg tablets	Supplied as a vialed liquid solution containing 500 mg (nominal) durvalumab per vial. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine hydrochloride, 275 mM trehalose dihydrate, 0.02% (w/v) polysorbate 80, at pH 6.0. The nominal fill volume is 10.0 mL.
Route of administration	Oral tablets	IV infusion
Dosing instructions: Please refer to Section 6.2 for study specific handling instructions	Patients enrolled in the study will receive 2 × 150 mg tablets BD. The 100 mg and 150 mg tablets will be used to manage dose reductions. An olaparib dose reduction to 200 mg BD is recommended for patients with moderate renal impairment (calculated creatinine clearance by Cockcroft-Gault equation of between 31 and 50 mL/min) (see Section 4.3.2.1).	Durvalumab 1500 mg via IV infusion Q4W ±2 days (fixed dosing for patients >30 kg body weight).

Packaging and labelling	Study drug will be provided in high-density polyethylene bottles with child-resistant closures. Labels will be prepared in accordance with GMP and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labeling. Label text will be translated into local language, as required. Olaparib will be provided with either single-panel labels or multi-language booklet labels. Specific dosing instructions will not be included on the label; the site must complete the "Patient Dispensing Card" with the details of the dosing instructions at the time of dispensing. The investigator's emergency contact details will not be on the label, but can be found in the informed consent and the 'Patient Dispensing Card'. For emergency purposes the patient must be in possession of the emergency contact details at all times.	Study drug will be provided in vials. Each vial will be labelled in accordance with GMP Annex 13 and per country regulatory requirement. Labels will be prepared in accordance with GMP and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language, as required. Durvalumab will be provided with either single-panel labels or multi-language booklet labels. The investigator's emergency contact details will not be on the label, but can be found in the informed consent and the 'Patient Emergency Card'. For emergency purposes, the patient must be in possession of the emergency contact details at all times.
Provider	AstraZeneca	AstraZeneca. Commercially available 0.9% (w/v) saline or 5% (w/v) dextrose IV bags will be supplied by each site.

BD twice daily; GMP Good Manufacturing Practice; IV intravenous(ly); Q4W every 4 weeks; w/v weight/volume

6.2 Preparation/handling/storage/accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study drugs received and any discrepancies are reported and resolved before use of the study drug.

Only patients enrolled in the study may receive study drugs and only authorised site staff may supply or administer study drugs. All study drugs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorised site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study drugs accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study drug are provided in the relevant appendices in the core protocol.

6.2.1 Durvalumab preparation and handling

Durvalumab will be supplied by AstraZeneca as a 500 mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine

hydrochloride, 275 mM trehalose dihydrate, and 0.02% (weight/volume [w/v]) polysorbate 80; it has a pH of 6.0 and a density of 1.054 g/mL. The nominal fill volume is 10.0 mL.

Study drug vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. The vials should be kept in the original packaging until use to prevent prolonged light exposure.

The dose of durvalumab for administration must be prepared by the investigator's or site's designated study drug manager using aseptic technique. Total time from needle puncture of the durvalumab vial to the start of administration should not exceed 4 hours at room temperature or 24 hours at 2°C to 8°C (36°F to 46°F). If the final product is stored at both refrigerated and ambient temperatures, the total time should not exceed 24 hours.

A dose of 1500 mg (for patients >30 kg body weight) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab concentration ranging from 1 to 15 mg/mL and delivered through an IV-administration set with a 0.2-µm or 0.22-µm filter. Add 30.0 mL (ie, 1500 mg) of durvalumab to an appropriately sized IV bag such that the final concentration is within 1 to 15 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

If a patient's body weight falls ≤30 kg during the study, (s)he will be withdrawn from the study treatment unless (s)he derives some clinical benefit according to the treating physician. In this case, and following agreement between the treating physician and the Sponsor, the patient may continue treatment at a body-weight adapted dose of 20 mg/kg actual body weight.

Weight-based dosing at 20 mg/kg (for patients ≤30 kg) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab concentration ranging from 1 to 15 mg/mL, and delivered through an IV administration set with a 0.2-µm or 0.22-µm filter. An example of a weight-based dose calculation is shown in Section 6.2.1.1.

Standard infusion time is one hour (±15 minutes), however if there are interruptions during infusion, the total allowed infusion time should not exceed 8 hours at room temperature.

If either preparation time or infusion time exceeds the time limits a new dose must be prepared from new vials. Durvalumab does not contain preservatives, and any unused portion must be discarded.

Do not co-administer other drugs through the same infusion line.

The IV line will be flushed with a volume of IV diluent equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered.

Durvalumab should be given at least 1 hour after the patient has taken their olaparib morning dose. Patients will be monitored before, during, and after the first durvalumab infusion with assessment of vital signs at the times specified in the SoA (Table 1) and Section 8.2.3 of the core protocol. If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be at the investigator's discretion (suggested 30 minutes after each durvalumab infusion). For management of patients who experience an infusion reaction, please refer to the toxicity and management guidelines for infusion-related reactions.

Durvalumab (1500 mg) will be administered via IV infusion Q4W ± 2 days. Treatment with durvalumab will commence on Day 1 following confirmation of eligibility and will continue on a Q4W schedule until disease progression is confirmed.

6.2.1.1 Durvalumab weight-based calculation

If a patient's body weight falls ≤30 kg during the study, (s)he will be withdrawn from the study treatment unless (s)he derives some clinical benefit according to the treating physician. In this case, and following agreement between the treating physician and the Sponsor, the patient may continue treatment at a body-weight adapted dose of 20 mg/kg of durvalumab Q4W until the weight improves to >30 kg, at which point the patient should start receiving the fixed dosing of durvalumab 1500 mg Q4W:

1 Cohort dose: X mg/kg
2 Patient weight: Y kg
3 Dose for patient: XY mg = X (mg/kg) × Y (kg)
4 Dose to be added into infusion bag:

Dose (mL) = XY mg/50 (mg/mL) where 50 mg/mL is durvalumab nominal concentration. The corresponding volume of durvalumab should be rounded to the nearest tenth mL (0.1 mL). Dose adjustments for each cycle are only needed for greater than 10% change in weight.

5 The number of vials required for dose preparation is the next greatest whole number of vials from the following formula:
Number of vials = Dose (mL) / 10.0 (mL/vial)

Example:

1 Cohort dose: 20 mg/kg
   (a) Patient weight: 30 kg
   (b) Dose for patient: 600 mg = 20 (mg/kg) × 30 (kg)
   (c) Dose to be added into infusion bag:
   Dose (mL) = 600 mg / 50 (mg/mL) = 12.0 mL

(d) The number of vials required for dose preparation:
Number of vials = 12.0 (mL) / 10.0 (mL/vial) = 2 vials

6.2.2 Olaparib preparation and handling

Olaparib is available as a film-coated tablet containing 150 or 100 mg of olaparib. Olaparib will be packed in high-density polyethylene bottles with child-resistant closures. The olaparib study treatment will be dispensed to patients. Each dosing container will contain sufficient medication for at least each treatment period plus overage. Multiple bottles of study treatment may be required for dispensing in order to make up the desired dose.

Patients will be administered olaparib tablets orally at a dose of 300 mg BD every day. The dose of 300 mg BD will be made up of 2×150 mg olaparib tablets, which should be taken at the same times each day, 12 ±2 hours apart with 1 glass of water. The tablets should be swallowed whole and not chewed, crushed, dissolved or divided. Olaparib tablets can be taken with or without food.

If vomiting occurs shortly after the study treatment tablets are swallowed, the dose should only be replaced if all of the intact tablets can be seen and counted. Should any patient enrolled on the study miss a scheduled dose for whatever reason (eg, as a result of forgetting to take the tablets or vomiting), the patient will be allowed to take the scheduled dose up to a maximum of 2 hours after that scheduled dose time. If greater than 2 hours after the scheduled dose time, the missed dose is not to be taken and the patient should take their allotted dose at the next scheduled time.

6.2.2.1 Renal impairment

If subsequent to study entry and while still on study therapy, a patient's estimated creatinine clearance (CrCl) falls below the threshold for study inclusion (≥51 mL/min), retesting should be performed promptly. An olaparib dose reduction is recommended for patients who develop moderate renal impairment (calculated CrCl by Cockcroft-Gault equation of between 31 and 50 mL/min) for any reason during the study: the dose of olaparib should be reduced to 200 mg BD.

Because the CrCl determination is only an estimate of renal function, in instances where the CrCl falls to between 31 and 50 mL/min, the investigator should use his or her discretion in determining whether a dose change or discontinuation of therapy is warranted. Olaparib has not been studied in patients with severe renal impairment (creatinine clearance ≤30 mL/min) or end-stage renal disease; if patients develop severe impairment or end-stage disease, it is recommended that olaparib be discontinued.

6.2.3 Study drug administration

It is important to follow the assessment schedule as closely as possible.

Patients should continue to receive study treatment (ie, durvalumab in combination with olaparib) until objective radiological disease progression as per Response Evaluation Criteria in Solid Tumours (RECIST 1.1), as long as, in the investigator's opinion, they are benefiting from treatment and they do not meet any other discontinuation criteria. Disease progression should be confirmed by a subsequent scan (no earlier than 4 weeks later) in the absence of clinically significant deterioration as assessed by the investigator. All patients who have objective progression of disease will enter follow-up.

6.2.4 Storage

All study drugs should be kept in a secure place under appropriate storage conditions.

The olaparib product label on the bottle specifies the appropriate storage. Storage is also described in the Investigator's Brochure.

Durvalumab is to be stored at the study centre in a secured facility with limited access and controlled temperature (2ºC to 8ºC). The temperature should be monitored on a daily basis and documented in the temperature monitoring log according to the study drug handling instructions.

The study drug must be kept in the original outer container and under conditions specified on the labels.

In the following cases, the centre staff should not use affected study drug and should immediately contact AstraZeneca representative for further guidance:

- Temperature excursion upon receipt or during storage at the study site
- Damaged kit upon receipt
- Damaged vial/bottle

Damaged study drug should be documented according to the instructions provided by AstraZeneca representative. Storage conditions stated in the Investigator's Brochure, or the study drug Handling Instructions document, may be superseded by the label storage.

6.2.5 Accountability

The study drugs provided for this study should be used only as directed in the study protocol.

The study site staff will account for all study drugs received at the centre, for unused study drugs, and for appropriate destruction (according to local procedures). Certificates of delivery, destruction, and/or return should be signed.

The administration of all medications (including study drug) and details of treatment with study drug should be recorded in the appropriate sections of the electronic Case Report Form (eCRF).

6.3 Measures to minimise bias: randomisation and blinding

This is an open-label study.

Recruitment to the biomarker-matched cohorts will be based upon a predefined schema (described in the Pathology and Genomic Testing Manual) for patient allocation which takes account of biomarker prevalence estimates and the platform of evidence for each study treatment.

Recruitment into the biomarker non-matched arms will be conducted in a sequential manner.

If a patient withdraws from participation in the study, then his/her enrolment code cannot be reused. Withdrawn patients will not be replaced.

6.4 Treatment compliance

The administration of all study drugs should be recorded in the appropriate sections of the eCRF. Durvalumab will be administered on site. Treatment compliance will be assured by reconciliation of site drug accountability logs. Patients will record their oral olaparib dosing on a diary which should be returned to the site at the next available visit. Sites should additionally record olaparib doses taken at site visits.

Patients will self-administer olaparib. Patients should be given clear instructions on how and when to take their study treatment. Study site staff will make tablet counts at regular intervals during treatment. Compliance will be assessed by the tablet count and the information will be recorded in the appropriate section of the eCRF. After the tablet count has been performed, the remaining tablets will not be returned to the patient but will be retained by the investigative site until reconciliation is completed by the study monitor. All patients must return their bottle(s) of olaparib at the appropriate scheduled visit, when a new bottle will be dispensed. Patients will be instructed to notify study site personnel of missed doses. Dates of missed or held doses will be recorded by the patient on their patient diary and by the site staff on the eCRF.

Patients must return all containers and any remaining tablets at the end of the study.

Any change from the dosing schedule, does interruptions, dose reductions, dose discontinuations should be recorded in the eCRF. Note: Dose reductions are not allowed for durvalumab (see Section 6.6).

The Study Drug Storage Manager is responsible for managing the study drug from receipt by the study site until the destruction or return of all unused study drug. The investigator(s) is/are responsible for ensuring that the patient has returned all unused study drug.

Use of study treatment in doses in excess of that specified in the protocol is considered to be an overdose. Refer to Section 8.4.3 for procedures in case of overdose.

6.5 Concomitant therapy

Any medication or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the patient is receiving at the time of enrolment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency.

Olaparib can inhibit CYP3A4 in vitro and is predicted to be a weak CYP3A inhibitor in vivo. Therefore, caution should be exercised when substrates of CYP3A4 are combined with olaparib, in particular those with a narrow therapeutic margin (eg, simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus, and quetiapine); please refer to Section 6.5.2.

Prohibited concomitant medications are described in Table 3. Please refer to Section 8.4.5 for guidance on management of study drug-related toxicities.

The use of concomitant medications must be recorded in the eCRF.

Table 3 Prohibited medications

Prohibited medication/class of drug:	
Unless stated otherwise, these medications are prohibited from the time that patients enter the main screening period until the last dose of study treatment. The pre-screen may be done whilst on prior therapy.	
Any investigational anticancer therapy other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment
Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment. (Note: concurrent use of hormones for non-cancer-related conditions [eg, insulin for diabetes and hormone replacement therapy] is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable [eg, by local surgery or radiotherapy]). Patients may receive treatment with bisphosphonates or RANKL inhibitors for the treatment of bone metastases

Table 3 Prohibited medications

Prohibited medication/class of drug:	
Immunosuppressive medications, including, but not limited to: systemic corticosteroids at doses exceeding 10 mg/day of prednisone or its equivalent, methotrexate, azathioprine, and tumour necrosis factor-α blockers	Should not be given concomitantly, or used for premedication prior to the infusions. The following are allowed exceptions: • Use of immunosuppressive medications for the management of study drug-related AEs • Short-term premedication for patients receiving combinations where the prescribing information for the agent requires the use of steroids for documented hypersensitivity reactions • Use in patients with contrast allergies • In addition, use of inhaled, topical, and intranasal corticosteroids is permitted. A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of non-immunotherapy related events experienced by the patient (eg, chronic obstructive pulmonary disease, radiation, nausea, etc).
Live attenuated vaccines	Prohibited from the time that patients enter the main screening period until 180 days after the last dose of study treatment.
Epidermal growth factor receptor (EGFR) Tyrosine kinase inhibitors (TKIs)	Should not be given concomitantly. Should be used with caution in the 90 days post last dose of durvalumab. Increased incidences of pneumonitis (with third generation EGFR TKIs) and increased incidence of transaminase increases (with 1st generation EGFR TKIs) have been reported when durvalumab has been given concomitantly.
Herbal and natural remedies which may have immune-modulating effects	Should not be given concomitantly unless agreed by the sponsor

AE adverse event

The use of herbal preparations/medications should be discouraged throughout the study. These herbal medications include, but are not limited to: St. John's Wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone, yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 7 days prior to first dose of study drug (3 weeks for St John's Wort). Use of these products, as well as use of all vitamins, nutritional supplements and all prescribed concomitant medications, must be recorded in the eCRF.

Other concomitant treatment

Medication other than that described above, which is considered necessary for the patient's safety and wellbeing, may be given at the discretion of the investigator and recorded in the appropriate sections of the eCRF.

6.5.1 Rescue and supportive medication

The study site will supply rescue medication and this will be procured locally. The sponsor will supply only if required by local regulations.

The use of rescue medications is allowable at any time during the study. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

Supportive medication, described in Table 4, may be given at the discretion of the investigator and recorded in the appropriate section of the eCRF.

Table 4 Supportive medication

Supportive medication/class of drug:	Usage:
Concomitant medications or treatments (eg, acetaminophen or diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care, except for those medications identified as "prohibited," as listed above	To be administered as prescribed by the investigator
Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy to non-target lesions, etc])	Should be used, when necessary, for all patients
Inactivated viruses, such as those in the influenza vaccine or authorised and approved COVID-19 vaccines	Permitted. Administration of COVID-19 vaccines should be avoided for 72 hours prior to administration of the first dose of study treatment.

COVID-19 Coronavirus Disease 2019.

6.5.2 Effect of olaparib on other drugs

Based on limited in vitro data, olaparib may increase the exposure to substrates of CYP3A, P-gp, organic anion-transporting protein (OATP)1B1, organic cation transporter (OCT)1, OCT2, OAT3, multi-drug and toxin extrusion protein (MATE)1 and MATE2K. Based on limited in vitro data, olaparib may reduce the exposure to substrates of 2B6, 2C9, 2C19 and P-gp. The efficacy of hormonal contraceptives may be reduced if co-administered with olaparib, please see Section 5.3.1 for instructions regarding use of contraception.

Caution should therefore be observed if substrates of these isoenzymes or transporter proteins are co-administered.

Examples of substrates include:

- CYP3A4 – hormonal contraceptive, simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and quetiapine
- CYP2B6 – bupropion, efavirenz
- CYP2C9 – warfarin
- CYP2C19 - lansoprazole, omeprazole, S-mephenytoin
- P-gp - simvastatin, pravastatin, digoxin, dabigatran, colchicine
- (OATP)1B1 - bosentan, glibenclamide, repaglinide, statins and valsartan
- OCT1, MATE1, MATE2K – metformin
- OCT2 - serum creatinine
- OAT3 - furosemide, methotrexate.

6.6 Dose modification and discontinuation

For patients who weigh >30 kg, the dose of durvalumab cannot be modified. If a patient's body weight falls ≤30 kg during the study, (s)he will be withdrawn from the study treatment unless (s)he derives some clinical benefit according to the treating physician. In this case, and following agreement between the treating physician and the Sponsor, the patient may continue treatment at a body-weight adapted dose of 20 mg/kg actual body weight.

Durvalumab dosing can be interrupted in the event of treatment-related toxicity. All toxicities will be graded according to Common Toxicity Criteria for Adverse Events (CTCAE)version 4.03. Dose reductions are not permitted. Please refer to the toxicity management guidelines for durvalumab.

Dose reductions (of olaparib only) or interruptions, and initiation of supportive care, are allowed as deemed appropriate by the treating physician. If Day 1 treatment with durvalumab is interrupted, then both study medications will be delayed until the combination can be resumed. The maximum interruption or cycle delay that is permitted is 28 days. Any patient requiring a toxicity related dose delay of more than 28 days from the intended day of the next scheduled dose must be discontinued from the study unless there is approval from the Study Physician for the patient to continue.

Olaparib can be dose reduced to 250 mg BD as a first step and to 200 mg BD as a second step (Table 5). If the reduced dose of 200 mg BD is not tolerable, no further dose reduction is allowed and study treatment should be discontinued. Once the dose is reduced, escalation is not permitted. In order to reduce the dose, new tablets will need to be dispensed.

Table 5 Olaparib dose reductions for toxicity management

Initial dose	Following rechallenge post-interruption: Dose reduction 1	Dose reduction 2
300 mg BD (2x150mg)	250 mg BD (1x150 mg and 1x100 mg)	200 mg BD (2x100 mg)

Please also refer to Section 4.3.2.1.

6.7 Treatment after the end of the study

Patients are permitted to either receive standard of care therapy, or to continue to receive study treatment following the end of the study if, in the opinion of the investigator, they are continuing to receive benefit from treatment. After discontinuation of study treatment, the investigator will be at liberty to define further most appropriate anti-cancer treatment. Subsequent anti-cancer treatment is expected to be initiated following the cancer recurrence or development of a new cancer. Information on subsequent anti-cancer therapies should be recorded on the clinical database.

7. DISCONTINUATION OF TREATMENT AND PATIENT WITHDRAWAL

Please refer to Section 7 in the core protocol. Guidance on re-allocation to a second treatment cohort is provided in Section 7.4 of the core protocol.

Study procedures and their timing for patients re-allocated to a second study treatment are summarised in the re-allocation SoA (Table 6). Note: From implementation of protocol version 10.0, optional re-allocation of patients to a second treatment cohort is no longer applicable.

Table 6 Schedule of Activities for patients re-allocated to second on-treatment period (Module 1)

	C1 28 days Weeks 1-4		**C2** 28 days Weeks 5-8		**C3** 28 days Weeks 9-12	**C4** 28 days Weeks 13-16	**C5 – etc** All cycles 28 days	**Study drug disc.** (28 days after study drug disc.)	**Safety follow-up** (90 days after study drug disc.)	**Survival follow up**	**Notes**
Week	**1**	**3**	**5**	**7**	**9**	**13**	**17, 21, 25, 29 etc**				
Cycle day	**1**	**15**	**1**	**15**	**1**	**1**	**1**				
Window (days)	**0**[a]	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±7**	**±7**	**±7**	
Study procedures											
Informed consent	X										Section 5.2.1 (core protocol). Patient must consent to new treatment. Will be performed within 28 days before dosing.
Eligibility criteria for re-allocation[b]	X										Patients must meet eligibility criteria in the core CSP (see Table 1) and in this module before dosing. Will be performed within 28 days before dosing.
Physical examination	X	X	X	X	X	X	X	X			Section 8.2.2 (core protocol)
Vital signs	X	X	X	X	X	X	X	X			Section 8.2.3 (core protocol)
ECG	X	As clinically indicated									Section 8.2.4 (core protocol)
Concomitant medications	X	X	X	X	X	X	X	X			Section 6.5
Laboratory assessments											
Clinical chemistry	X	X	X	X	X	X	X	X			Section 8.2.1 (core protocol). If screening laboratory assessments are performed within 3 days prior to Day 1 they do not need to be repeated at Day 1
Haematology	X	X	X	X	X	X	X	X			
APTT and INR		As clinically indicated									
TSH, free T_3, and free T_4	X	X	X	X	X	X	X	X			Section 8.2.1 (core protocol)

	C1 28 days Weeks 1-4		**C2** 28 days Weeks 5-8		**C3** 28 days Weeks 9-12	**C4** 28 days Weeks 13-16	**C5 – etc** All cycles 28 days	**Study drug disc.** (28 days after study drug disc.)	**Safety follow-up** (90 days after study drug disc.)	**Survival follow up**	**Notes**
Week	**1**	**3**	**5**	**7**	**9**	**13**	**17, 21, 25, 29 etc**				
Cycle day	**1**	**15**	**1**	**15**	**1**	**1**	**1**				
Window (days)	**0**[a]	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±7**	**±7**	**±7**	
Urinalysis		As clinically indicated									Section 8.2.1 (core protocol)
Pregnancy test	X		X		X	X	X	X			Section 8.2.1.2 (core protocol)
AE/SAE assessment	X	X	X	X	X	X	X	X	X		Section 8.3 (core protocol)
Study drug administration											
Durvalumab	X		X		X	X	X				Section 6.2.1
Olaparib	X		X		X	X	X				Section 6.2.2
Drug accountability	X	X	X	X	X	X	X	X			Section 6.2.5
Other assessments											
Subsequent cancer therapy									X	X	These assessments are repeated here from Table 1. Patients will be followed for survival from the original treatment cohort. These are not additional assessments for re-allocation, they are only repeated here for completeness.
Survival status										X	

[a] Every effort should be made to minimise the time between allocation to treatment and starting treatment.
[b] Eligibility criteria in core CSP and in this module apply

Note, if main screening assessments have been performed within 3 days prior to C1D1, then assessments do not need to be performed on C1D1 pre-dose.
Note, from implementation of protocol v10.0, optional re-allocation of patients to a second treatment cohort is no longer applicable.
AE adverse event; APTT activated partial thromboplastin time; C cycle; ECG electrocardiogram; INR international normalised ratio; SAE serious adverse event; TSH thyroid-stimulating hormone; T_3 triiodothyronine; T_4 thyroxine.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in the SoA (Table 1). Study procedures and their timing for patients re-allocated to a second study treatment are summarised in the re-allocation SoA (Table 6).

8.1 Efficacy assessments

Please refer to the core protocol.

8.2 Safety assessments

8.2.1 Clinical safety laboratory assessments

Please refer to core protocol.

8.2.1.1 Coagulation

Please refer to core protocol.

8.2.1.2 Other safety assessments

Monthly pregnancy tests are required for treatments with olaparib. Pregnancy tests will be done on Day 1 of every cycle in Module 1 (see Table 1 and Table 6). See Section 8.2.1.2 in the core protocol for details of the pregnancy test.

8.2.1.3 Pneumonitis (interstitial lung disease) investigation

The following assessments, and additional assessments if required, will be performed to enhance the investigation and diagnosis of potential cases of pneumonitis. The results of the assessment will be collected.

- Physical examination; Signs and symptoms (cough, shortness of breath and pyrexia, etc) including auscultation for lung field will be assessed.
- SpO_2; Saturation of peripheral oxygen (SpO_2)
- Other items; When pneumonitis (interstitial lung disease [ILD]) is suspected during study treatment, the following markers should be measured where possible:
  - ILD markers (KL-6, SP-D) and β-D-glucan
  - Tumour markers: Particular tumour markers which are related to disease progression.

8.2.2 Physical examinations

Please refer to core protocol.

8.2.3 Vital signs

Please refer to core protocol.

8.2.4 Electrocardiograms

Please refer to core protocol.

8.2.5 Performance status

Please refer to core protocol.

8.3 Collection of adverse events

Please refer to the core protocol.

8.4 Safety reporting and medical management

8.4.1 Reporting of serious adverse events

Please refer to the core protocol.

8.4.2 Pregnancy

Please refer to the core protocol.

8.4.3 Overdose

Please refer to the core protocol.

8.4.4 Medication error

Please refer to the core protocol.

8.4.5 Management of study drug-related toxicities

At this time, there are limited safety data regarding the combination of durvalumab and olaparib. Given the differing mechanisms of action of durvalumab and olaparib, the potential for potentiation of toxicities is thought to be limited. Some toxicities, for example pneumonitis and asthenia/fatigue may, on theoretical grounds, be potentiated in the combination arm and particular attention should be paid to these.

In the event of toxicity in this combination arm of the study which cannot be managed by supportive measures alone, stopping one or both medications should be an investigator decision based on the available information and, if necessary, following discussion with the sponsor.

The following general guidance should be followed for management of toxicities:

- Treat each of the toxicities with maximum supportive care (including withholding the agent suspected of causing the toxicity if required).
- If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of the assigned study drug along with appropriate continuing

supportive care. If medically appropriate, dose modifications are permitted for olaparib. In addition, guidelines on olaparib dose modifications are provided in Section 6.6. In the event of toxicity that cannot be managed by following the toxicity management guidelines for olaparib and durvalumab, consider stopping treatment with olaparib.

All dose modifications should be documented with clear reasoning and documentation of the approach taken. Dose reductions are not permitted without prior agreement with the study physician.

8.4.5.1 Management of durvalumab-related toxicities

Please refer to the toxicity management guidelines for durvalumab.

8.4.5.2 Management of olaparib-related toxicities

Any toxicity observed during the course of the study could be managed by interruption of the dose of olaparib or dose reductions. Please refer to Section 6.6.

Management of haematological toxicity

The management of anaemia is presented in Table 7.

Table 7 Management of anaemia

Haemoglobin level	Action to be taken
Hb <10 but ≥8 g/dL (CTCAE Grade 2)	**First occurrence:** Give appropriate supportive treatment and investigate causality. Investigator judgement to continue olaparib with supportive treatment (eg, transfusion) or interrupt dose for a maximum of 4 weeks. Study treatment can be restarted if Hb has recovered to > 9g/dL. Subsequent occurrences: If repeat Hb <10 but ≥ 9 g/dL, investigator judgement to continue olaparib with supportive treatment (eg transfusion) or dose interrupt (for a maximum of 4 weeks) until Hb >9 g/dL and upon recovery dose reduction may be considered to 250 mg BD as a first step and to 200 mg BD as a second step. If Hb < 9 *but* ≥ 8 g/dL, dose interrupt (for max of 4 weeks) until Hb ≥ 9 g/dL and upon recovery dose reduction may be considered (to 250 mg BD as a first step and to 200 mg BD as a second step).
Hb <8 g/dL (CTCAE Grade 3)	Give appropriate supportive treatment (eg, transfusion) and investigate causality. Interrupt olaparib for a maximum of 4 weeks until improved to Hb ≥ 9 g/dL. Upon recovery dose reduce to **250 mg BD** as a first step and to **200 mg BD** as a second step in the case of repeat Hb decrease.

BD twice daily; CTCAE Common Terminology Criteria for Adverse Events; Hb haemoglobin.

Common treatable causes of anaemia (eg, iron, vitamin B12 or folate deficiencies and hypothyroidism) should be investigated and appropriately managed. In some cases, management of anaemia may require blood transfusions. For cases where patients develop

prolonged haematological toxicity (≥2-week interruption/delay in study treatment due to CTCAE Grade 3 or worse anaemia and/or development of blood transfusion dependence), further information relating to management of prolonged haematological toxicities while on study treatment can be found later in this section.

Management of neutropenia, leukopenia and thrombocytopenia

The management of neutropenia, leukopenia, and thrombocytopenia is presented in Table 8.

Table 8 Management of neutropenia, leukopenia, and thrombocytopenia

Toxicity	Study treatment dose adjustment
CTCAE Grade 1 to 2	Investigator judgement to continue treatment or if dose interruption, this should be for a maximum of 4 weeks; appropriate supportive treatment and causality investigation.
CTCAE Grade 3 to 4	Dose interruption until recovered to CTCAE Grade 1 or better for a maximum of 4 weeks. If repeat CTCAE Grade 3-4 occurrence, dose reduce olaparib to 250 mg BD as a first step and 200 mg BD as a second step.

BD: twice daily; CTCAE: Common Terminology Criteria for Adverse Events.

Adverse events of neutropenia and leukopenia should be managed as deemed appropriate by the investigator with close follow-up and interruption of study drug if CTCAE Grade 3 or worse neutropenia occurs. Platelet transfusions, if indicated, should be done according to local hospital guidelines.

Primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) is not recommended, however, if a patient develops febrile neutropenia, study treatment should be stopped and appropriate management including G-CSF should be given according to local hospital guidelines. Please note that G-CSF should not be used within at least 24 hours (7 days for pegylated G-CSF) of the last dose of study treatment unless absolutely necessary. For cases where patients develop prolonged haematological toxicity (≥2-week interruption/delay in study treatment due to CTCAE Grade 3 or worse), refer to guidance below.

Management of prolonged haematological toxicities while on study treatment

If a patient develops prolonged haematological toxicity such as:

- ≥2-week interruption/delay in study treatment due to CTCAE Grade 3 or worse anaemia and/or development of blood transfusion dependence
- ≥2-week interruption/delay in study treatment due to CTCAE Grade 3 or worse neutropenia (absolute neutrophil count $<1 \times 10^9$/L)
- ≥2-week interruption/delay in study treatment due to CTCAE Grade 3 or worse thrombocytopenia and/or development of platelet transfusion dependence (platelets $<20 \times 10^9$/L).

Check weekly differential blood counts including reticulocytes and peripheral blood smear. If any blood parameters remain clinically abnormal after 4 weeks of dose interruption, the patient should be referred to a haematologist for further investigations. Bone marrow analysis and/or blood cytogenetic analysis should be considered at this stage according to standard haematological practice. Study treatment should be discontinued if blood counts do not recover to CTCAE Grade 1 or better within 4 weeks of dose interruption.

Development of a confirmed MDS or other clonal blood disorder should be reported as a serious adverse event (SAE) and full reports must be provided by the investigator to AstraZeneca, Patient Safety. Olaparib treatment should be discontinued if patient's diagnosis of MDS and/or AML is confirmed.

Management of non-haematological toxicity

Repeat dose interruptions are allowed as required, for a maximum of 4 weeks on each occasion. If the interruption is any longer than this the study physician must be informed. Where toxicity reoccurs following rechallenge with study treatment, and where further dose interruptions are considered inadequate for management of toxicity, then the patient should be considered for dose reduction or must permanently discontinue study treatment.

Olaparib can be dose reduced to 250 mg BD as a first step and to 200 mg BD as a second step. Treatment must be interrupted if any CTCAE Grade 3 or 4 AE occurs, which the investigator considers to be related to administration of study treatment.

Management of new or worsening pulmonary symptoms

If new or worsening pulmonary symptoms (eg, dyspnoea) or radiological abnormalities occur in the absence of a clear diagnosis, an interruption in study treatment dosing is recommended and further diagnostic workup (including a high resolution computed tomography [CT] scan) should be performed to exclude pneumonitis. Following investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, then study treatment can be restarted, if deemed appropriate by the investigator. If significant pulmonary abnormalities are identified, these need to be discussed with the study physician.

Management of nausea and vomiting

Events of nausea and vomiting are known to be associated with olaparib treatment. In Study D0810C00019 (NCT00753545), nausea was reported in 71% of the olaparib-treated patients and 36% in the placebo-treated patients and vomiting was reported in 34% of the olaparib-treated patients and 14% in the placebo-treated patients. These events are generally mild to moderate (CTCAE Grade 1 or 2) severity, intermittent and manageable on continued treatment. The first onset generally occurs in the first month of treatment for nausea and

within the first 6 months of treatment for vomiting. For nausea, the incidence generally plateaus at around 9 months, and for vomiting at around 6 to 7 months.

No routine prophylactic anti-emetic treatment is required at the start of study treatment, however, patients should receive appropriate anti-emetic treatment at the first onset of nausea or vomiting and as required thereafter, in accordance with local and international treatment practice guidelines. Alternatively, olaparib tablets can be taken with a light meal/snack (ie, 2 pieces of toast or a couple of biscuits).

Interruptions for intercurrent non-toxicity related events

Olaparib has not been studied in patients with severe renal impairment (creatinine clearance ≤30 mL/min) or end-stage renal disease; if patients develop severe impairment or end-stage disease is it recommended that olaparib treatment be discontinued.

Study treatment dose interruption for conditions other than toxicity resolution should be kept as short as possible. If a patient cannot restart study treatment within 4 weeks for resolution of intercurrent conditions not related to disease progression or toxicity, the case should be discussed with the AstraZeneca study physician.

All dose reductions and interruptions (including any missed doses), and the reasons for the reductions/interruptions are to be recorded in the eCRF.

Study treatment should be stopped at least 3 days prior to planned surgery. After surgery, study treatment can be restarted when the wound has healed. No stoppage of study treatment is required for any needle biopsy procedure.

Study treatment should be discontinued for a minimum of 3 days before a patient undergoes radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.

Because the AEs related to olaparib may include asthenia, fatigue and dizziness, patients should be advised to use caution while driving or using machinery if these symptoms occur.

8.4.6 Adverse events of special interest

Adverse events of special interest (AESIs) are events of scientific and medical interest specific to understanding of the study drug profile and may require close monitoring. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterise and understand them in association with the use of this study drug.

The AESIs for durvalumab are summarised in core protocol Section 8.3.12.

The AESIs for olaparib are the important identified risk of MDS/AML, the important potential risk of new primary malignancy (other than MDS/AML) and the potential risk of pneumonitis.

A questionnaire will be sent to any investigator reporting an AESI, as an aid to provide further detailed information on the event. During the study, there may be other events identified as AESIs that require the use of a questionnaire to help characterise the event and gain a better understanding regarding the relationship between the event and study treatment.

8.5 Pharmacokinetics

Please refer to the core protocol.

8.6 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7 Genetics

Please refer to the core protocol.

8.8 Biomarkers

Please refer to the core protocol.

8.9 Medical Resource Utilisation and Health Economics

Health Economics/Medical Resource Utilisation and Health Economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

Please refer to the core protocol.

10. REFERENCES

Chatzinikolaou et al 2014
Chatzinikolaou G, Karakasilioti I, Garinis GA. DNA damage and innate immunity: links and trade-offs. Trends Immunol. 2014;35(9):429-35.

Farmer et al 2005
Farmer H, McCabe N, Lord CJ, Tutt ANJ, Johnson DA, Richardson TB et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Letter to Nature. 2005 (April 14);434:917-921.

Higuchi et al 2015
Higuchi T, Flies DB, Marjon NA, Mantia-Smaldone G, Ronner L, Gimotty PA, Adams SF. CTLA-4 Blockade Synergizes Therapeutically with PARP Inhibition in BRCA1-Deficient Ovarian Cancer. Cancer Immunol Res. 2015 Nov;3(11):1257-68.

Huang et al 2015
Huang J, Wang L, Cong Z, Amoozgar Z, Kiner E, Xing D et al. The PARP1 inhibitor BMN 673 exhibits immunoregulatory effects in a Brca1(-/-) murine model of ovarian cancer. Biochem Biophys Res Commun. 2015 Aug 7;463(4):551-6.

Garassino et al 2017
Garassino M, Vansteenkiste J, Joo-Hang K, Hervé L, Mazières J, Powderly J et al. Durvalumab in ≥3rd-Line Locally Advanced or Metastatic, EGFR/ALK Wild-Type NSCLC: Results from the Phase 2 ATLANTIC Study. J Thor Onc. 2017;12:S10-S11.

Kroemer et al 2013
Kroemer G, Galluzzi L, Kepp O, Zitvogel L. Immunogenic cell death in cancer therapy. Annu Rev Immunol. 2013;31:51-72.

Koyama et al 2016
Koyama S, Akbay EA, Li YY, Aref AR, Skoulidis F, Herter-Sprie GS et al. STK11/LKB1 Deficiency Promotes Neutrophil Recruitment and Proinflammatory Cytokine Production to Suppress T-Cell Activity in the Lung Tumor Microenvironment. Cancer Res. 2016;76(5):999-1008.

Ledermann et al 2014
Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial. Lancet Oncol. 2014;15(8):852-61.

Lee et al 2017
Lee JM, Cimino-Mathews A1, Peer CJ, Zimmer A, Lipkowitz S, Annunziata CM et al. Safety and Clinical Activity of the Programmed Death-Ligand 1 Inhibitor Durvalumab in Combination with Poly (ADP-Ribose) Polymerase Inhibitor Olaparib or Vascular Endothelial Growth Factor Receptor 1-3 Inhibitor Cediranib in Women's Cancers: A Dose-Escalation, Phase I Study. J Clin Oncol. 2017;35:2193-2202.

Mateo et al 2015
Mateo J, Carreira S, Sandhu S, Miranda S, Mossop H, Perez-Lopez R. DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer. N Engl J Med. 2015;373(18):1697-708.

Mateo et al 2016
Jateo J, Moreno V, Gupta A, Kaye SB, Dean E, Middleton MR et al. An adaptive study to determine the optimal dose of the tablet formulation of the PARP inhibitor olaparib. Targ Oncol. 2016;11:401–415.

Mulligan et al 2014
Mulligan JM, Hill LA, Deharo S, Irwin G, Boyle D, Keating KE et al. Identification and validation of an anthracycline/cyclophosphamide-based chemotherapy response assay in breast cancer. J Natl Cancer Inst. 2014;106(1):djt335.

Narwal et al 2013
Narwal R, Roskos LK, Robbie GJ. Population Pharmacokinetics of Sifalimumab, an Investigational Anti-Interferonalpha Monoclonal Antibody, in Systemic Lupus Erythematosus. Clin Pharmacokinet. 2013;52:1017–27.

Ng et al 2006
Ng CM, Lum BL, Gimenez V, Kelsey S, Allison D. Rationale for fixed dosing of pertuzumab in cancer patients based on population pharmacokinetic analysis. Pharm Res. 2006;23(6):1275–84.

O'Connor 2015
O'Connor MJ. Targeting the DNA Damage Response in Cancer. Mol Cell. 2015;60(4):547-60.

Parkes et al 2016
Parkes EE, Walker SM, Taggart LE, McCabe N, Knight LA, Wilkinson R et al. Activation of STING-Dependent Innate Immune Signaling By S-Phase-Specific DNA Damage in Breast Cancer. J Natl Cancer Inst. 2016;109(1). pii: djw199. Print 2017 Jan.

Pommier et al 2016
Pommier Y, O'Connor MJ, de Bono J. Laying a trap to kill cancer cells: PARP inhibitors and their mechanisms of action. Sci Transl Med. 2016;8(362):362ps17. Erratum in: Sci Transl Med. 2016 Dec 7;8(368):368er7

Rizvi et al 2015
Rizvi NA, Hellmann MD, Snyder A, Kvistborg P, Makarov V, Havel JJ et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science. 2015;348(6230).

Skoulidis et al 2017
Skoulidis F, Hellman MD, Awad M, Gainor JF, Rizvi H, Carter B et al. LKB1 loss is a novel genomic predictor of de novo resistance to PD-1/PD-L1 axis blockade in KRAS-mutant lung adenocarcinoma. Annals Oncol. 2017; 28(Suppl_5)

Tang et al 2014
Tang ML, Khan MK, Croxford JL, Tan KW, Angeli V Gasser S. The DNA damage response induces antigen presenting cell-like functions in fibroblasts. Eur J Immunol. 2014;44(4):1108-18.

Wang et al 2009
Wang DD, Zhang S, Zhao H, Men AY, Parivar K. Fixed dosing versus body size based dosing of monoclonal antibodies in adult clinical trials. J Clin Pharmacol. 2009;49(9):1012–24.

Wang et al 2016
Wang YS, Chen J, Cui F, Wang H, Wang S, Hang W et al. LKB1 is a DNA damage response protein that regulates cellular sensitivity to PARP inhibitors. Oncotarget. 2016;7(45):73389-73401.

Zhang et al 2012
Zhang S, Shi R, Li C, Parivar K, Wang DD. Fixed dosing versus body size-based dosing of therapeutic peptides and proteins in adults. J Clin Pharmacol. 2012;52(1):18–28.

Clinical Study Protocol

Drug Substances	Umbrella study
Study Code	D6185C00001 (HUDSON)
Version	14.0
Date	09 October 2024

Appendix J

Module 2: Durvalumab plus AZD9150

An Open-Label, Multi-Drug, Biomarker-Directed, Multi-Centre Phase II Umbrella Study in Patients with Non-Small Cell Lung Cancer, who Progressed on an Anti-PD-1/PD-L1 Containing Therapy (HUDSON)

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

Regulatory Agency Identification Numbers:

EudraCT number: 2017-002208-28

EU CT number: 2023-509004-15-00

IND number: 138050

VERSION HISTORY

Version 14.0, 09 October 2024
Key amendments and rationale for changes: The version number of this module has been revised in line with the other modules in the HUDSON study; however, no changes have been made to this module.

Version 13.0, 14 December 2023
Key amendments and rationale for changes: **Front page:** EU CT number has been added in line with the core CSP.

Version 12.0, 01 March 2023
Key amendments and rationale for changes: The version number of this module has been revised in line with the other modules in the HUDSON study; however, no changes have been made to this module.

Version 11.0, 16 August 2022
Key amendments and rationale for changes: The version number of this module has been revised in line with the other modules in the HUDSON study; however, no changes have been made to this module.

Version 10.0, 12 April 2022
Key amendments and rationale for changes: The version number of this module has been revised in line with the other modules in the HUDSON study; however, no changes have been made to this module.

Version 9.0, 14 May 2021
Key amendments and rationale for changes: The version number of this module has been revised in line with the other modules in the HUDSON study; however, no changes have been made to this module.

Version 8.0, 11 September 2020
The version number of this module has been revised in line with the other modules in the HUDSON study; however, no changes have been made to this module.

Version 7.0, 21 May 2020
Key amendments and rationale for changes: Module 2 (HUDSON) ***Module 2 completed enrolment in May 2019 and all patients had completed study treatment in October 2019. In April 2020, as a result of a comprehensive review of data from the AZD9150 (danvatirsen) programme, AstraZeneca made the strategic decision to discontinue development of AZD9150 due to limited efficacy above what is expected from durvalumab in recent clinical studies. The safety profile of AZD9150 has not changed. Hence no further changes will be made to this module.***

Version 6.0, 05 November 2019
Key amendments and rationale for changes: **Table 1 Schedule of Activities:** Footnote added that ad-hoc collection of survival status may be requested for OS analyses. **Section 2.2.1.2 Durvalumab data:** Text updated to align with Edition 15 of the durvalumab IB. **Section 2.2.2 AZD9150:** Text updated to align with Edition 10 of the AZD9150 IB. **Figure 2 Study flow diagram:** Updated to reflect the addition of Modules 6 and 7.

Section 4.3.1 Justification of durvalumab dose: Correction of typographical errors and to align with Edition 15 of the durvalumab IB.

Section 6.2.1 Durvalumab preparation and handling: Change to the window around the duration of durvalumab infusion to ±15 minutes. The previous window of ±5 minutes was considered too restrictive.

Table 4 Prohibited medications: Information on the rationale for the prohibition of EGFR TKIs added.

Section 8.4.7 Adverse events of special interest: New section created for the AESIs for clarity. Changes made to the text to align with changes being made in the core protocol.

Version 5.0, 19 March 2019

Key amendments and rationale for changes:

Table 1 Schedule of Activities – Treatment intervention period (Module 2):

- Clarified that tumour evaluation scans are required until objective disease progression, up to and including the 90-day safety follow-up period.
- Updated in line with the core protocol, to replace modified RECIST 1.1 with RECIST 1.1, to ensure comparability with other NSCLC study results. Updated for consistency across all modules of the study.

Figure 1 Study design: Updated to clarify that patients with locally advanced disease are included, and to specify ctDNA at pre-screening.

Section 2 Introduction and **Section 4.1 Overall design:** Amended in line with inclusion criterion 5 in the core clinical study protocol (CSP), which clarified the required prior treatment in response to questions from investigators. According to the study's main objective, patients must have had disease progression on a prior anti-PD-1/PD-L1 therapy. The patient must have also received a prior platinum doublet though it is not required to have had disease progression whilst receiving treatment with the platinum doublet therapy.

Section 2.1 Study rationale: Clarification that there is currently no established therapy for patients who have developed resistance to PD-1/PD-L1 and platinum-doublet therapies.

Section 2.2 Background: Product name 'danvatirsen' added in line with IB, and indication text updated to reflect status of approvals for durvalumab (IB Edition 14, 11 February 2019).

Section 2.2.1.1 Overview of durvalumab: Indication text updated to reflect status of approvals for durvalumab (IB Edition 14, 11 February 2019).

Section 2.2.1.2 Durvalumab data: PACIFIC overall survival data and Study CD-ON-MEDI4736-1108 efficacy data updated in line with the IB for durvalumab (Edition 14, 11 February 2019).

Section 2.2.2.2 AZD9150 data and **Section 8.4.5.2 Management of AZD9150-related toxicities:** Potential risks updated to reflect the known safety profile of AZD9150.

The following sections have been updated in line with the core durvalumab Clinical Study Protocol (CSP), in which the Toxicity Management Guidelines (TMGs) for durvalumab have been removed from the main body of the CSP template and moved to a standalone annex. TMG versioning will be independent of the protocol allowing for consistency across the durvalumab clinical development programme.

- Updated for consistency across all modules of the study.
- Section 6.2.1 Durvalumab preparation and handling
- Section 6.6 Dose modification and discontinuation
- Section 8.4.5.1 Management of durvalumab-related toxicities
- Section 8.4.6.1 Toxicity management guidelines for combination therapy (durvalumab plus AZD9150)

Figure 2 Study flow diagram: Footnote added to specify that per protocol version 3.0, Module 4 (durvalumab + vistusertib) is closed to recruitment.

Section 5.3.1 Restrictions applicable to durvalumab: Noted that topical corticosteroids are permitted.

Section 6.2.1 Durvalumab preparation and handling: Updated for clarity and alignment with product insert.

Section 6.2.3 Study drug administration: Updated in line with the core protocol, to replace modified RECIST 1.1 with RECIST 1.1, to ensure comparability with other NSCLC

study results. Time window for infusion of AZD9150 added for consistency with other modules. **Section 6.4 Treatment compliance** and **Section 6.6 Dose modification and discontinuation:** Clarified that dose reductions are not allowed for durvalumab without prior agreement with the study physician. **Section 6.6 Dose modification and discontinuation:** Text changed from 'temporary discontinuation' to 'treatment interruption' for clarity. **Section 6.6 Dose modification and discontinuation** and **Section 8.4.5.2 Management of AZD9150-related toxicities:** Updated to clarify the time point from which treatment interruption is measured (i.e. the date of the next scheduled dose). **Table 6 Schedule of Activities – re-allocated to second on-treatment period (Module 2):** Updated to clarify that informed consent and screening period to confirm eligibility for re-allocation will be performed within 28 days before dosing and to cross refer to the eligibility criteria in Table 1 of the core CSP. Module 2 (HUDSON) **Section 8.4.6 Durvalumab and AZD9150 combination:** Clarification that the potential risk of increases in AST/ALT when durvalumab is given in combination with AZD9150, is based on the knowledge that both drugs may cause increases, albeit by different mechanisms of action.
Version 4.0, 26 October 2018
Updated version number to keep in line with changes made in the core CSP. No other changes were made in this appendix.
Version 3.1, 31 July 2018
Key amendments and rationale for changes: **Table 1 Schedule of Activities:** Update to the durvalumab ADA sampling schedule in response to a request from the FDA. Sampling is still required pre-dose on Cycle 1 Day 1 and Cycle 2 Day 1, but is now also subsequently required Q12W within the first year and Q24W in the second year of treatment. Addition of a ±7 day window around the study discontinuation and follow-up visits. Removal of WHO/ECOG assessments: these will now only be performed at screening to reduce the burden on sites. **Section 2.2 Background:** Updates to durvalumab and AZD9150 background information in light of emerging data.

Figure 2 Flow diagram: Updated to reflect the addition of Module 5 to the protocol.

Section 5.3.1 Restrictions applicable to durvalumab: Amended to extend the period patients should not receive live vaccines to 180 days after the last dose of study drug. Updated for consistency across all modules of the study.

Section 6.2.2 AZD9150 preparation and handling: Removal of the requirement to use a filter when administering AZD9150, in light of emerging data from an in-use stability study.

Table 4 Prohibited medications: Updated to align with updated exclusion criteria in the core protocol.

Section 6.6 Dose modification and discontinuation: Text moved from the module to the core protocol and amended to allow patients to continue receiving treatment with monotherapy if, in the opinion of the treating physician, they are deriving benefit.

Table 6 Schedule of Activities – re allocated to second on treatment period (Module 2): Addition of a ±7 day window around the study discontinuation and follow-up visits. Removal of WHO/ECOG assessments: these will now only be performed at screening to reduce the burden on sites.

Section 8.2.3 Vital signs: Clarification of timing of assessments.

Section 8.4.5 Management of study drug-related toxicities: Clarified that following dose reduction, AZD9150 dose cannot be re-escalated.

Version 2.0, 26 February 2018

Key amendments and rationale for changes:

IND number updated following advice from the FDA to conduct HUDSON under its own IND, which cross references IND 119833.

Table 1 Schedule of activities updated to include the requirement for:

- Pregnancy tests, for women of child bearing potential, on day 1 of every cycle, whilst the patient is on treatment.
- Vital signs to be taken before AZD9150 infusions (added footnote).

Figure 1 Study design: For patients who are re-allocated to a second treatment within HUDSON, the "screening assessments as per schedule of assessments in the treatment

specific module" was corrected to state "as per schedule of assessments **in the core protocol**".

2.2.1 Durvalumab: Background information added in line with the new durvalumab IB Edition 12.

2.2.2 AZD9150: Addition of up-to-date background information.

Figure 2 Study flow diagram: Based on observations from other studies exploring the hypothesis of TORC1/2 inhibition, *TSC1* and *TSC2* have been removed as biomarkers of interest in HUDSON.

4.3.1 Justification for durvalumab dose: information added on dose justification in line with the durvalumab IB Edition 12.

5.3 Lifestyle restrictions: Blood donation guidance updated to be in line with the new durvalumab IB Edition 12.

6.2.2.1 Intravenous dose preparation and administration: Corrected the stability of AZD9150 from 2 hours to 4 hours at room temperature.

6.2.3 Administration of AZD9150: Added that AZD9150 dose should be skipped if outside of the allowable time frames.

6.6 Dose modification and discontinuation: Clarification of dose modification and discontinuation rules, including:

- If patient's body weight falls ≤30 kg during the study, (s)he will be withdrawn from the study treatment unless (s)he derives some clinical benefit according to the treating physician. This text was also added to section **6.2.1.1 Durvalumab weight-based calculation** for clarity.
- Management of dose interruptions and discontinuation of durvalumab and AZD9150.

Table 6 Schedule of activities for re-allocation of treatment:

- Updated to include the requirement for pregnancy tests, for women of child bearing potential, on day 1 of every cycle, whilst the patient is on treatment.
- Footnote added to clarify that eligibility criteria for both core CSP and this module are applicable.
- Footnote added for vital signs to be taken before AZD9150 infusions.

8.4.5.2 Management of AZD9150-related toxicity: Clarification of toxicity management rules.

8.4.6.1 Toxicity management guidelines for combination therapy (durvalumab plus AZD9150): Clarified that patient cannot continue on AZD9150 monotherapy if treatment with durvalumab is discontinued. If AZD9150 treatment is discontinued for more than 21 days, the patient should permanently discontinue study treatment.

10. References: Updated in line with the additional background information provided on AZD9150 in section 2.2.2.

Various administrative changes.

Version 1.0, 05 September 2017
Initial Creation

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

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1. PROTOCOL SUMMARY

1.1 Schedule of Activities (SoA)

The Schedule of Activities (SoA) for the lead-in and on-treatment period of Module 2 is shown in Table 1 below, and for the optional re-allocated second on-treatment period in Section 7, Table 6. For the SoA for the pre-screening and main screening visits, please refer to the core protocol.

Table 1 Schedule of Activities – Treatment intervention period (Module 2)

	C0 (Table 3)			C1 (28 days) Weeks 1-4				C2 (28 days) Weeks 5-8				C3 – etc All cycles 28 days				Study drug disc. (28 days after study drug disc.)	Safety follow-up (90 days after study drug disc.)	Survival follow-up	Notes
Week	**One week lead-in**			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**				
Day of cycle	**1**	**3**	**5**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**				
Window (days)	**+1[a]**			**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±7**	**±7**	**±7**	
Study procedures																			
Physical examination	X			X		X		X		X		X				X			Section 8.2.2 (core protocol)
Vital signs[b]	X			X		X		X		X		X				X			Section 8.2.3 (core protocol)
ECG				X	As clinically indicated														Section 8.2.4 (core protocol)
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			Section 6.5
Laboratory assessments																			
Clinical chemistry	X			X		X		X		X		X				X			Section 8.2.1 (core protocol). If screening laboratory assessments are performed within 3 days prior to C0D1 they do not need to be repeated at C0D1.
Haematology	X			X		X		X		X		X				X			
APTT and INR					As clinically indicated														
TSH, free T_3, and free T_4	X			X		X		X		X		X				X			Section 8.2.1 (core protocol)
Urinalysis					As clinically indicated														Section 8.2.1 (core protocol)
Pregnancy test	X			X				X				X				X			Section 8.2.1.2 (core protocol)
AE/SAE assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Section 8.3 (core protocol)
Study drug administration																			
Durvalumab				X				X				X							Section 6.2.3

Table 1 Schedule of Activities – Treatment intervention period (Module 2)

	C0 (Table 3)			**C1** (28 days) Weeks 1-4				**C2** (28 days) Weeks 5-8				**C3 – etc** All cycles 28 days				**Study drug disc.** (28 days after study drug disc.)	**Safety follow-up** (90 days after study drug disc.)	**Survival follow-up**	**Notes**
Week	**One week lead-in**			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**				
Day of cycle	**1**	**3**	**5**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**				
Window (days)	**+1[a]**			**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±7**	**±7**	**±7**	
AZD9150	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				Section 6.2.3
Drug accountability	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			Section 6.2.5
Other laboratory assessments and assays																			
Blood for ctDNA assessments	X			X		X		X		X		X				X			Section 8.8 (core protocol)
Circulating soluble factors (plasma)	X			X		X		X								X			Section 8.8 (core protocol). These should also be taken at Cycle 4, Day 1 (Week 13)
Whole blood for gene expression (PAXgene RNA tubes)	X			X		X		X								X			Section 8.8 (core protocol). These should also be taken at Cycle 4, Day 1 (Week 13).
PBMCs for flow cytometry (activation by / PD-1 CD8+)~	X			X		X		X											Section 8.8 (core protocol). These should also be taken at Cycle 4, Day 1 (Week 13).
TCR immuno-sequencing	X			X		X		X											Section 8.8 (core protocol). These should also be taken at Cycle 4, Day 1 (Week 13).
Blood sample for AZD9150 PK analysis (pre- and post-dose except at discontinuation)	X		X			X		X								X			Section 8.5 (core protocol). These should also be taken at Cycle 4, Day 1 (Week 13).

Table 1 Schedule of Activities – Treatment intervention period (Module 2)

	C0 (Table 3)			C1 (28 days) Weeks 1-4				C2 (28 days) Weeks 5-8				C3 – etc All cycles 28 days				Study drug disc. (28 days after study drug disc.)	Safety follow-up (90 days after study drug disc.)	Survival follow-up	Notes
Week	**One week lead-in**			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**				
Day of cycle	**1**	**3**	**5**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**				
Window (days)	**+1[a]**			**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±7**	**±7**	**±7**	
Blood sample for ADA for durvalumab (pre-dose except at safety follow up)				X				X				X (C5D1) then Q12W in first year, then Q24W in second year					X		Section 8.5.3 (core protocol)
Blood sample for ADA for AZD9150 (pre-dose except at discontinuation)	X		X			X		X								X			Section 8.5.3 (core protocol). These should also be taken at Cycle 4, Day 1 (Week 13).
Tumour evaluation (CT or MRI) (RECIST 1.1)				Every 6 weeks ±1 week for the first 24 weeks relative to the start of combination therapy (Cycle 1, Day 1), and then every 8 weeks (±1 week) thereafter, until objective disease progression as defined by RECIST 1.1 and confirmed with a subsequent scan (in the absence of clinically significant deterioration)															Section 8.1 (core protocol)
Biopsy on-treatment (mandatory)										X									Section 8.8 (core protocol). This should align with the first RECIST assessment.
Biopsy on disease progression (mandatory only for re-allocated patients)																X			Section 8.8 (core protocol)
Subsequent cancer therapy																	X	X	Section 8.1.3.1 (core protocol). Every 3 months
Survival status																		X[c]	Section 8.1.3.1 (core protocol). Every 3 months

[a] Every effort should be made to minimise the time between allocation to treatment and starting treatment. Note, if main screening assessments have been performed within 3 days prior to C0D1, then assessments do not need to be performed on C0D1 pre-dose.

[b] Vital signs to be taken prior to AZD9150 infusion and as per core CSP section 8.2.3

[c] Ad hoc collection of survival status may be requested for overall survival analyses

ADA anti-drug antibodies; AE adverse event; APTT activated partial thromboplastin time; C cycle; CD8+ cytotoxic T-cell; CT computed tomography; ctDNA circulating tumour DNA; D day; ECG electrocardiogram; INR international normalised ratio; RECIST 1.1 Response Evaluation Criteria in Solid Tumours 1.1; MRI magnetic resonance imaging; PBMC peripheral blood mononuclear cell; PD-1 programmed cell death-1; PK pharmacokinetics; Q12W every 12 weeks; Q24W every 24 weeks; SAE serious adverse event; TCR T-cell receptor repertoire; TSH thyroid-stimulating hormone; T_3 triiodothyronine; T_4 thyroxine.

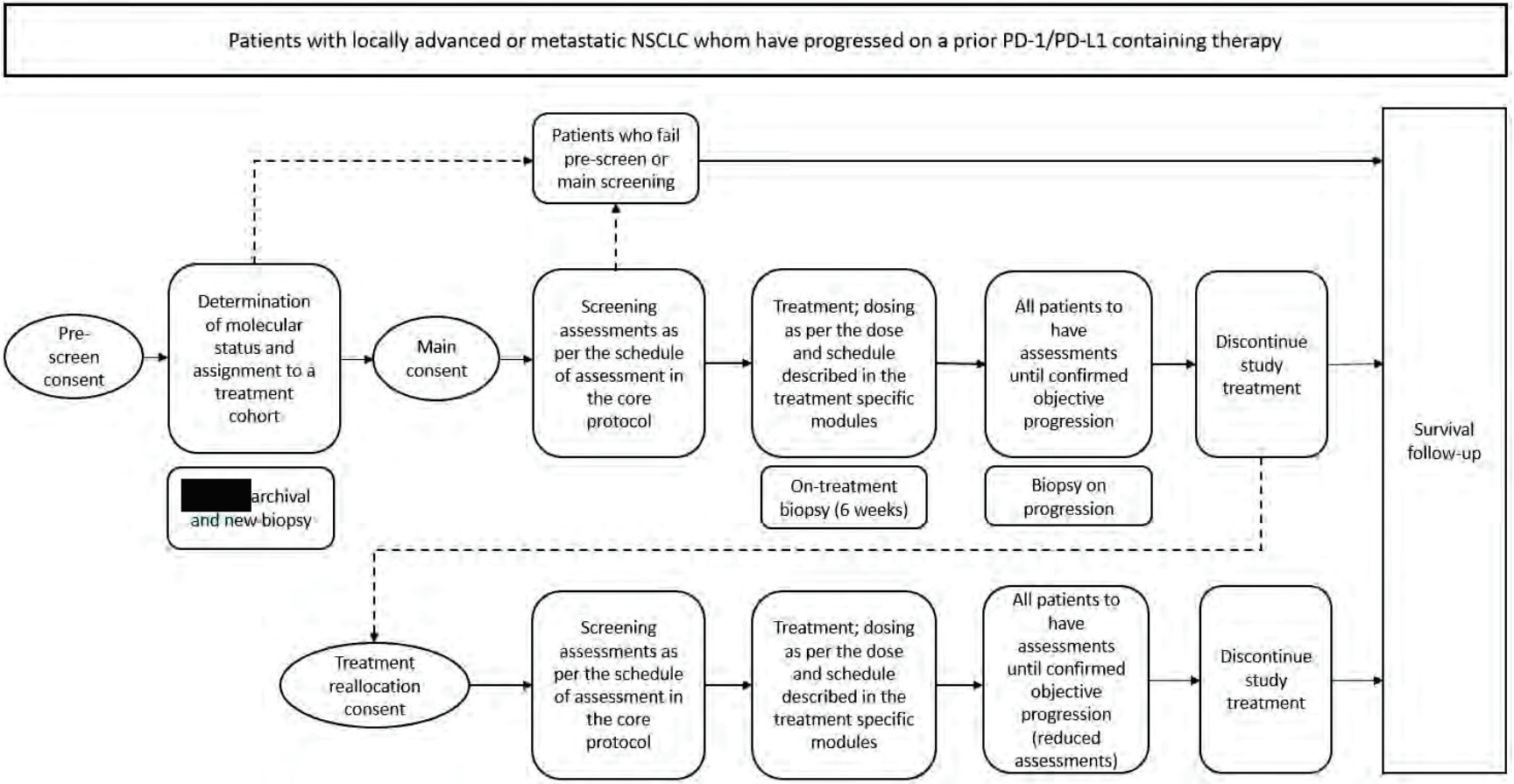
1.2 Synopsis

Please refer to Section 1.2 of the core protocol.

1.3 Schema

The general study design is summarised in Figure 1.

Figure 1 Study design



ctDNA circulating tumour DNA; NSCLC non-small cell lung cancer; PD-1 programmed cell death 1; PD-L1 programmed cell death ligand 1

2. INTRODUCTION

NOTE: Module 2 completed enrolment in May 2019 and all patients had completed study treatment in October 2019. In April 2020, as a result of a comprehensive review of data from the AZD9150 (danvatirsen) programme, AstraZeneca made the strategic decision to discontinue development of AZD9150 due to limited efficacy above what is expected from durvalumab in recent clinical studies. The safety profile of AZD9150 has not changed. Hence no further changes will be made to this module.

Study D6185C00001 (HUDSON) is a Phase II, open-label, multi-centre umbrella study in patients who have received an anti-programmed cell death-1 (PD-1)/anti-programmed cell death-ligand 1 (PD-L1) containing therapy and a platinum-doublet regimen for locally advanced or metastatic non-small cell lung cancer (NSCLC) either separately or in combination. The patient must have had disease progression on a prior line of anti-PD-1/PD-L1 therapy. The modular design allows the evaluation of the efficacy, safety, and tolerability of multiple study drugs. This module to the core study protocol describes Module 2, which will investigate the efficacy, safety, and tolerability of durvalumab administered in combination with AZD9150.

2.1 Study rationale

As described in Section 2.2 of the core protocol, immune checkpoint inhibitors targeting the PD-1/PD-L1 pathway have shown significant activity in the first- and second-line treatment settings in patients with NSCLC. However, it is becoming evident that there is a new and significant patient population emerging that does not respond to anti-PD-1/anti-PD-L1 containing therapy (primary resistance) or progresses during anti-PD-1/anti-PD-L1 containing therapy (acquired resistance). There is currently no established therapy for patients who have developed resistance to PD-1/PD-L1 and platinum-doublet therapies, and novel treatments for these patients are urgently needed.

The aim of this umbrella study (D6185C00001) is to investigate multiple study drugs for the treatment of NSCLC in molecularly matched and non-matched patient populations after failure of immune checkpoint inhibitors, to identify patient populations who may respond favourably to novel anti-tumour therapies.

2.2 Background

Durvalumab and AZD9150 (Note: per IB, AZD9150 is also known as danvatirsen) are both currently in clinical development as anti-cancer therapies in a variety of malignancies.

Durvalumab (IMFINZI) 50 mg/mL was first approved for the treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) in the United States (US) on 1 May 2017. On 16 February 2018, durvalumab was approved in the US for the treatment of patients

with unresectable Stage III NSCLC. On 21 September 2018, durvalumab was approved in the European Union (EU) for the treatment of locally advanced, unresectable NSCLC in adults whose tumours express PD-L1 on ≥1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy. As of 12 July 2019, durvalumab is approved in 18 countries for UC and over 45 countries for NSCLC.

Module 2 will investigate both agents in combination, to test the hypothesis that the combination will result in complementary anti-tumour activity.

Combining the PD-L1 inhibitor durvalumab with an agent targeting immunosuppression in the tumour microenvironment (AZD9150) is a complementary anti-tumour strategy, as the 2 study drugs may restore effective anti-tumour immunity at 2 distinct stages: promoting the effector function of T-cell responses (durvalumab) while hindering immune escape in the tumour immune microenvironment (AZD9150).

Brief background on AZD9150 and durvalumab is provided below. For detailed descriptions of the chemistry, pharmacology, efficacy, and safety of AZD9150 and durvalumab, refer to the respective Investigator's Brochures.

2.2.1 Durvalumab

2.2.1.1 Overview of durvalumab

Expression of PD-L1 protein is an adaptive immune response that helps tumours evade detection and elimination by the immune system. PD-L1 can be induced by inflammatory signals (eg, interferon-gamma) and can be expressed on both tumour cells and tumour-associated immune cells in tumour microenvironment. PD-L1 blocks T-cell function and activation through interaction with PD-1 and CD80 (B7.1). By binding to its receptors, PD-L1 reduces cytotoxic T-cell activity, proliferation, and cytokine production. Durvalumab is a fully human, high affinity, immunoglobulin G1 kappa monoclonal antibody that selectively blocks the interaction of PD-L1 with PD-1 and cluster of differentiation (CD)80 (B7.1) while leaving PD-1/ programmed cell death ligand-2 interaction intact. Durvalumab does not induce antibody dependent cell-mediated cytotoxicity. Selective blockade of PD-L1/PD-1 and PD-L1/CD80 interactions enhances antitumour immune responses. These antitumour responses may result in tumour elimination.

Durvalumab is approved in a number of territories including the US, EU, Japan, Canada and Brazil under the brand name IMFINZI™ Injection.

The recommended dose as per the IMFINZI package insert is 10 mg/kg administered as an IV infusion over 60 minutes every 2 weeks (Q2W).

For more information, please refer to the latest version of the Durvalumab Investigator's Brochure.

2.2.1.2 Durvalumab data

To date, durvalumab has been given to more than 8800 patients as part of ongoing studies either as monotherapy or in combination with other anticancer agents. Details on the safety profile of durvalumab monotherapy are summarized below. Refer to the current durvalumab IB for a complete summary of pre-clinical and clinical information including safety, efficacy, and pharmacokinetics (PK).

Clinical activity in locally advanced NSCLC

The efficacy of durvalumab was evaluated in the PACIFIC Study, a randomised, double-blind, placebo-controlled, multicentre study in 713 patients with histologically or cytologically confirmed locally advanced, unresectable NSCLC. Patients had completed definitive platinum-based chemoradiation within 1 to 42 days prior to initiation of the study and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Ninety-three percent of patients had received a total dose of 54 to 66 Gy of radiation. The study excluded patients who had progressed following concurrent chemoradiation therapy, patients with active or prior documented autoimmune disease within 2 years of initiation of the study; a history of immunodeficiency; a history of severe immune-mediated adverse reactions; medical conditions that required systemic immunosuppression, except physiological dose of systemic corticosteroids; active tuberculosis or hepatitis B or C or HIV infection or patients receiving live attenuated vaccine within 30 days before or after the start of durvalumab. Patients were randomised 2:1 to receive 10 mg/kg durvalumab (n=476) or 10 mg/kg placebo (n=237) via IV infusion Q2W for up to 12 months or until unacceptable toxicity or confirmed disease progression. Randomisation was stratified by gender, age (<65 years vs. ≥65 years) and smoking status (smoker vs. nonsmoker). Patients with disease control at 12 months were given the option to be re-treated upon disease progression. Tumour assessments were conducted every 8 weeks for the first 12 months and then every 12 weeks thereafter.

The demographics and baseline disease characteristics were well balanced between study arms. Baseline demographics of the overall study population were as follows: male (70%), age ≥65 years (45%), White (69%), Asian (27%), other (4%), current smoker (16%), past-smoker (75%), and never smoker (9%), World Health Organisation (WHO)/ECOG PS 0 (49%), WHO/ECOG PS 1 (50%). Disease characteristics were as follows: Stage IIIA (54%), Stage IIIB (44%), histological subgroups of squamous (47%), non-squamous (53%), PD-L1 expression in tumour cells (TC)≥25% (22%), PD-L1 expression TC<25% (41%). (PD-L1 status was retrospectively analysed using the Ventana PD-L1 [SP263] Assay in 451 patients with available samples, taken prior to concurrent chemoradiation therapy).

At the time of the interim progression-free survival (PFS) analysis, the median PFS by blinded independent central review (BICR) was significantly longer with durvalumab treatment (16.8 months) compared with placebo (5.6 months); hazard ratio 0.52; 98.9% CI: 0.39, 0.70; p<0.0001. At the time of the interim overall survival (OS) analysis, the median OS was not

reached for the durvalumab arm and was 29.1 months for the placebo arm; hazard ratio, 0.69; 95% CI, 0.55, 0.86). The 36-month OS rate was 57.0% with durvalumab vs 43.5% with placebo.

Clinical activity in recurrent and metastatic NSCLC

Based on current data from the ongoing Study CD ON MEDI4736-1108 (NCT01693562), evidence of clinical activity with durvalumab has been observed. The following responses were observed in patients with NSCLC.

Overall, clinical activity was observed in both the PD-L1 high (defined as having tumour cells [TC] ≥25%) and PD-L1 low/negative (defined as TC <25%) subgroups, however, patients with PD-L1 high tumours had higher objective response rates (ORRs).

The ORR per BICR was 21.8% and 6.4% in patients with PD-L1 high and low/negative tumours, respectively and 15.3% in the overall population regardless of PD-L1 expression. The ORR was 25.9%, 14.3% and 11.5% in the 1L, 2L and 3L+ cohorts, respectively. Median duration of response (DOR) was 17.74 months. Median OS was 12.4 months; median OS was 21.0, 11.8 and 9.3 months in the 1L, 2L and 3L+ cohorts, respectively. The OS rate at 24 months was 29.6%.

The ATLANTIC study in third-line or higher NSCLC showed higher ORR and survival outcomes in high PD-L1 positive patients. Across cohorts the ORR ranged from 3 to 43%, median PFS ranged from 1.8 to 5.5 months and median OS ranged from 5.9 to 13.6 months but was not reached at the time of initial reporting in the >90% PD-L1 expressors. The ORR and survival outcomes reported in durvalumab studies are in keeping with other similar agents targeting the PD-1/PD-L1 axis (Garassino et al 2017).

Preliminary efficacy data from the MYSTIC study in first-line advanced or metastatic NSCLC showed that in PD-L1 high (≥25% TC) NSCLC, median PFS by BICR was 4.7 months for durvalumab monotherapy and 5.4 months for chemotherapy; hazard ratio of 0.87; 99.5% CI: 0.593, 1.285; p=0.324. The median OS was 16.3 months for the durvalumab arm and 12.9 months for the chemotherapy arm; hazard ratio for death was 0.76; 97.54% CI: 0.564, 1.019; p=0.036. The 24-month OS rate was 38.3% vs 22.7% and the 12-month PFS rate was 32.3% vs 14.3% for the durvalumab and chemotherapy arms respectively. When durvalumab was administered in combination with tremelimumab, the median PFS by BICR was 3.9 months for durvalumab + tremelimumab and 5.4 months for chemotherapy; hazard ratio of 1.05; 99.5% CI: 0.722, 1.534; p=0.705. The median OS was 11.9 months for the durvalumab + tremelimumab arm and 12.9 months for the chemotherapy arm; hazard ratio for death was 0.85; 98.77% CI: 0.611, 1.173; p=0.202. The 24-month OS rate was 35.4% vs 22.7% and the 12-month PFS rate was 25.8% vs 14.3% for the durvalumab + tremelimumab and chemotherapy arms respectively.

Immuno-oncology agents targeting the PD-1/PD-L1 pathway have demonstrated activity as monotherapy and in combination with chemotherapy in patients who are immunotherapy-naïve. However, the present study will recruit patients who either have primary resistance to anti-PD-1/PD-L1 therapy or who developed acquired resistance while on anti-PD-1/PD-L1 therapy. Thus, in this immunotherapy-resistant setting, durvalumab will be administered in combination with an agent that has a different and complementary mechanism of action in order to maximise the likelihood of clinical activity.

2.2.2 AZD9150

2.2.2.1 Overview of AZD9150

AZD9150 is a 16-nucleotide anti-sense oligonucleotide (ASO) designed to target and indirectly down-regulate the expression of human signal transducer and activator of transcription 3 (STAT3) protein by down-regulating STAT3 messenger RNA (mRNA). The STAT3 protein belongs to the STAT family of transcription factors and is considered to be a promising cancer drug target because of its pleiotropic involvement in tumourigenesis. STAT3 regulates the expression of many genes directly important to the survival of tumour cells (Alvarez et al 2005), but it is also an important factor in non-tumour cells of the tumour microenvironment involved in immune evasion of tumour cells, angiogenesis, and metastasis (Kordylewski et al 2009).

Responses to checkpoint inhibitors may be significantly limited by an immune suppressive tumour microenvironment, of which STAT3 is a well-established regulator (Wang et al 2004, Avalle et al 2012, Kortylewski and Yu 2008, Yu et al 2007, Villerino et al 2017). In particular, STAT3 signalling in immune cells of the tumour microenvironment is known to suppress antitumour immunity (Kortylewski et al 2005). Consistent with this, monotherapy using the STAT3-specific antisense molecule AZD9150 has been associated with clinical responses reminiscent of immune-mediated antitumour effects (Hong et al 2015). Further, AZD9150 elicits changes in gene expression signatures that are associated with better responses to PD-1 axis inhibitors (McCoon et al 2015, Ribas et al. 2015, Ayers et al 2015). These findings suggest that combination of STAT3 and PD-1 pathway inhibitors may prove synergistic. Preclinical results in several mouse models lend strong support to this idea: STAT3 ASO treatment has been shown to reduce intratumoral numbers of immune-suppressive CD163+ and ARG1+ cells and to enhance anti-tumour responses to PD-L1 antibody treatment, including induction of tumour regressions and associated immunological memory (Woessner et al. 2016, Woessner et al. 2017).

Under normal biological conditions, STAT3 activation is rapid and transient; however, aberrant activation of STAT3 is associated with many human cancers including lymphoma, glioblastoma, ovarian cancer, and hepatocellular carcinoma (Al Zaid Siddiquee and Turkson 2008).

Interactions between tumour cells, immune cells, and other cell types within the tumour microenvironment have a significant impact on the progression of cancer. Tumour cells respond to the sum total of the signals within the local tumour microenvironment emanating from inflammatory cells, fibroblasts, and endothelial cells, which release cytokines, chemokines, and growth factors to stimulate tumour growth and modulate the invasive potential of tumour cells. These signals also create immunosuppressive networks that enable immune evasion of tumour cells (Yu et al 2007). STAT3 drives the production of interleukin IL-6, IL-10, and vascular endothelial growth factor (VEGF) from tumour cells, and also regulates the production of pro-tumourigenic and anti-tumourigenic cytokines produced from immune cells. Thus, STAT3 establishes a critical crosstalk between tumour cells and tumour-associated immune cells and is a central component of a 'feed-forward loop' that shifts the tumour microenviroment to a more pro-tumourigenic phenotype (Yu et al 2007; Kordylewski et al 2009).

This data supports the view of STAT3 as a critical regulator of numerous functions important in cancer and that inhibition of STAT3 in tumour cells and in non-tumour stromal cells will likely lead to benefit for cancer patients. Following systemic administration, the primary mechanism of AZD9150 is to reduce STAT3 mRNA and protein levels in tumour cells and in non-tumour stromal cells. Non-clinical and clinical data with AZD9150 available to date support STAT3 as a viable cancer drug target and demonstrate that AZD9150 warrants further clinical study in patients with advanced solid malignancies.

AZD9150 is therefore under investigation by AstraZeneca for the treatment of patients with advanced cancers, including advanced/metastatic squamous cell carcinoma of the head and neck (SCCHN), diffuse large B-cell lymphoma (DLBCL), muscle invasive bladder cancer, NSCLC and relapsed/refractory aggressive Non-Hodgkin's lymphoma. Currently, AZD9150 is being evaluated as a combination treatment with other immuno-oncology drugs as well as chemotherapeutic agents.

2.2.2.2 AZD9150 data

As summarised in the AZD9150 Investigator's Brochure, exposure to AZD9150 in clinical studies to date includes approximately 428 patients with advanced solid tumours or lymphoma who have received doses from 1 to 4 mg/kg in AstraZeneca-sponsored studies and 19 additional patients treated in investigator-initiated studies.

AZD9150 has shown efficacy in DLBCL with tumour responses observed among the lymphoma subset of 40 patients: 2 achieved complete response (CR) and 2 achieved partial response (PR) for an overall response rate (ORR) of 10.0%. The median (95% CI) duration of their response was 11.65 months (10.67, 12.63). In the overall population of 55 patients, an additional 3 patients achieved stable disease.

Evidence of limited anti-tumour activity of AZD9150 was observed in the study population of patients with advanced or metastatic HCC in Study D5660C00001. One patient achieved a PR that was sustained until Week 54 and 10 (25.6%) patients had a best response of stable disease.

Combination studies with durvalumab, and other agents, are ongoing. Details are summarised in the IB. No formal analysis of efficacy has been conducted.

Together, the extensive non-clinical data, durability of responses already observed in patients with AZD9150 (DLBCL, HCC), and the tolerable safety profile of AZD9150 which is well managed with the existing toxicity management guidelines, strongly support the further evaluation of AZD9150 as a therapeutic, for patients with advanced malignancies, either alone or in combination.

Potential risks with AZD9150

Thrombocytopenia/platelet count decreases and liver enzyme elevations (ALT/AST) are important identified risks with AZD9150. Important potential risks are: reduced haemoglobin/anaemia and reduced absolute neutrophil count/neutropenia. Potential class effects associated with other phosphorothioate oligonucleotides have included renal and hepatic effects. There is also a theoretical risk for the development of autosomal dominant hyper IgE syndrome (AD-HIES), a rare disorder thought to be associated with mutations in STAT3 and a reduction in STAT3 levels. More detailed information about the known and expected benefits and risks and reasonably expected AEs of AZD9150 can be found in the Investigator's Brochure.

2.3 Benefit/risk assessment

As described in Section 2.3 of the core protocol, patients recruited to this study are not expected to have other treatment options apart from monotherapy chemotherapy, such as docetaxel. The survival outcome and toxicity profile of chemotherapy in this setting mean that other active therapies are highly desirable and present a potential advantage for patients.

The study design aims to identify patient populations who may respond favourably to novel anti-tumour therapies. Based upon the available non-clinical and clinical safety data, the limited survival benefit provided by the currently available treatment options to patients, the limited life expectancy due to malignant disease, and the hypothesis of the complementary effect of the 2 agents, the investigation of the potential therapeutic efficacy of the combination of durvalumab with AZD9150 in patients with advanced or metastatic NSCLC is acceptable, and the overall benefit/risk assessment supports the proposed study design. A proposed benefit to seeking signals by this biomarker stratification strategy includes the opportunity to discover potential increased sensitivity to the study drugs under evaluation.

3. OBJECTIVES AND ENDPOINTS

Please refer to core protocol.

4. STUDY DESIGN

4.1 Overall design

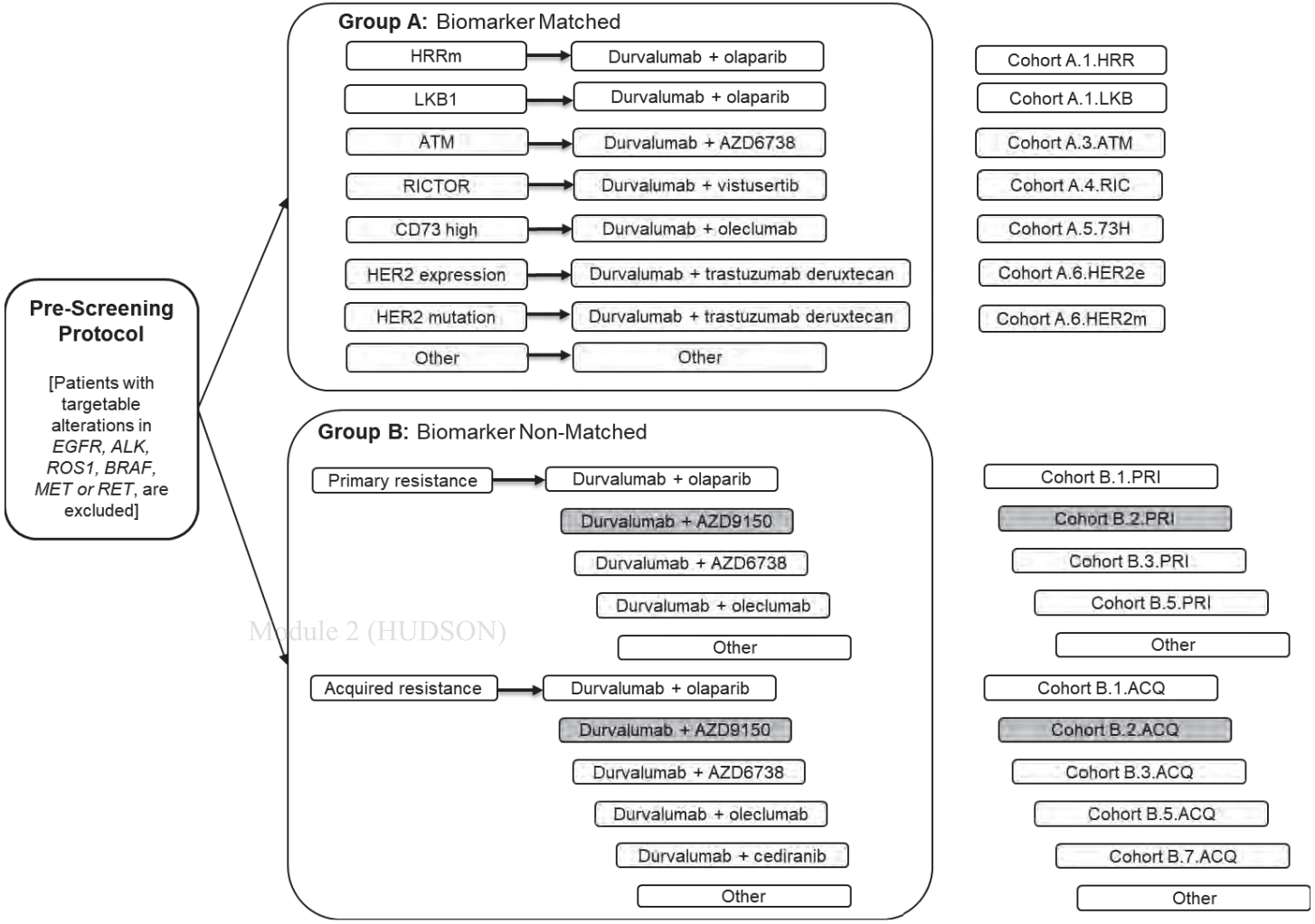
This is an open-label, multi-centre, umbrella study in patients who have received an anti-PD-1/PD-L1 containing therapy and a platinum-doublet regimen for locally advanced or metastatic NSCLC either separately or in combination. The patient must have had disease progression on a prior line of anti-PD-1/PD-L1 therapy. For an overview of the study design see Figure 1; further details on the overall design are provided in Section 4 of the core protocol. For details on the study drugs given in Module 2, see Section 6.1 of this module.

Module 2 will investigate the efficacy, safety, and tolerability of durvalumab in combination with AZD9150 (both given intravenously [IV]) in Cohorts B.2, and includes patients who are either primary resistant (Cohort B.2.PRI), or developed acquired resistance while on prior anti-PD-1/PD-L1 containing immunotherapy (Cohort B.2.ACQ). These terms are defined as follows:

- Primary resistance; patients who had anti-PD-1/PD-L1 containing therapy but had progression of disease (PD) within ≤24 weeks from the start of treatment.
- Acquired resistance; patients who had progressive disease >24 weeks from the start of anti PD-1/PD-L1 containing therapy whilst still on that treatment.

A study flow diagram is provided in Figure 2. The treatment cohorts described in this module are highlighted in grey.

Figure 2 Study flow diagram



Note, per protocol version 3.0, Module 4 (durvalumab + vistusertib) is closed to recruitment.
ACQ patients with acquired resistance; *ATM* ataxia telangiectasia mutated; CD73 cluster of differentiation 73; HER2 human epidermal growth factor receptor 2; *HRRm* mutation detected in a homologous recombination repair; *LKB1* liver kinase B1 (also known as *STK11*; serine threonine kinase 11); PRI patients with primary resistance; *RICTOR* rapamycin-insensitive companion of mechanistic target of rapamycin (mTOR) complex-2.

4.2 Scientific rationale for study design

The study aims to identify patient populations who may respond favourably to novel anti-tumour therapies, and the modular design allows evaluation of the efficacy, safety, and tolerability of multiple study drugs. The study requires an open-label design owing to the different schedules and routes of administration of the study drugs.

4.3 Justification for dose

4.3.1 Justification for durvalumab dose

A durvalumab dose of 20 mg/kg Q4W is supported by in vitro data, pre-clinical activity, clinical PK/pharmacodynamics, biomarkers, and activity data from Study CD-ON-MEDI4736-1108 (hereafter referred to as Study 1108) in patients with advanced solid tumors and from a Phase I study performed in Japanese patients with advanced solid tumor (D4190C00002).

PK/Pharmacodynamic data

Based on available PK/pharmacodynamic data from ongoing Study 1108 with doses ranging from 0.1 to 10 mg/kg Q4W or 15 mg/kg Q4W, durvalumab exhibited non-linear (dose-dependent) PK consistent with target-mediated drug disposition. The PK approached linearity at ≥3 mg/kg Q4W, suggesting near complete target saturation (membrane-bound and sPD-L1), and further shows that the durvalumab dosing frequency can be adapted to a particular regimen given the linearity seen at doses higher than 3 mg/kg. The expected half-life with doses ≥3 mg/kg Q4W is approximately 21 days. A dose-dependent suppression in peripheral sPD-L1 was observed over the dose range studied, consistent with engagement of durvalumab with PD-L1. A low level of immunogenicity has been observed. No patients have experienced immune-complex disease following exposure to durvalumab. (For further information on immunogenicity, please see the current durvalumab IB).

A population PK model was developed using the data from Study 1108 (doses=0.1 to 10 mg/kg Q2W or 15 mg/kg Q4W; Fairman et al 2014). Multiple simulations indicate that a similar overall exposure is expected following both 10 mg/kg Q4W and 20 mg/kg Q4W regimens, as represented by AUC_{ss} (4 weeks). Median $C_{max,ss}$ is expected to be higher with 20 mg/kg Q4W (~1.5 fold) and median $C_{trough,ss}$ is expected to be higher with 10 mg/kg Q4W (~1.25 fold). Clinical activity with the 20 mg/kg Q4W dosing regimen is anticipated to be consistent with 10 mg/kg Q4W with the proposed similar dose of 20 mg/kg Q4W expected to (a) achieve complete target saturation in majority of patients; (b) account for anticipated variability in PK, pharmacodynamics, and clinical activity in diverse cancer populations; (c) maintain sufficient PK exposure in case of antidrug antibody (ADA) impact; and (d) achieve PK exposure that yielded maximal antitumor activity in animal models.

Given the similar area under the serum drug concentration-time curve (AUC) and modest differences in median peak and trough levels at steady state, the observation that both regimens maintain complete sPD-L1 suppression at trough, and the available clinical data, the 20 mg/kg Q4W and 10 mg/kg Q4W regimens are expected to have similar efficacy and safety profiles, supporting further development with a dose of 20 mg/kg Q4W.

Clinical data

Refer to the current durvalumab IB for a complete summary of clinical information including safety, efficacy, and PK at the 20 mg/kg Q4W regimen.

Rationale for fixed dosing

A population PK model was developed for durvalumab using monotherapy data Study 1108 (N=292; doses = 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W; solid tumors). Population PK analysis indicated only minor impact of body weight on the PK of durvalumab (coefficient of ≤0.5). The impact of body weight-based (10 mg/kg Q2W) and fixed dosing (750 mg Q2W) of durvalumab was evaluated by comparing predicted steady state PK concentrations (5th, median, and 95th percentiles) using the population PK model. A fixed dose of 750 mg was selected to approximate 10 mg/kg (based on median body weight of ~75 kg). A total of 1000 patients were simulated using body weight distribution of 40 to 120 kg. Simulation results demonstrate that body weight-based and fixed dosing regimens yield similar median steady state PK concentrations with slightly less overall between-patient variability with fixed dosing regimen.

Similar findings have been reported by others (Narwal et al 2013, Ng et al 2006, Wang et al 2009, Zhang et al 2012). Wang and colleagues investigated 12 monoclonal antibodies and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies (Wang et al 2009). In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-patient variability in PK/pharmacodynamic parameters (Zhang et al 2012).

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar PK exposure and variability, AstraZeneca considered it feasible to switch to fixed dosing regimens. Based on average body weight of 75 kg, a fixed dose of 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) is included in the current study.

An exception to 1500 mg fixed dosing is made for patients with low body weight (below 30 kg). Patients with a body weight of 30 kg or less must receive weight-based dosing, equivalent to 20 mg/kg, until weight increases to greater than 30 kg. At this time, fixed dosing data for patients weighing below 30 kg (corresponding to doses greater than 50 mg/kg) are not available and are not yet supported by product development.

Thus, the clinical activity observed coupled with the safety profile, translational science correlates, and non-clinical data supports further development with a dose of 1500 mg Q4W. The dose of durvalumab will not be modified during the study.

4.3.2 Justification for AZD9150 dose

AZD9150 was dosed in ongoing trials on an ideal body weight (IBW) basis as the apparent volume of distribution for oligonucleotides does not increase proportionately to body weight in obese patients or patients who weigh substantially less than their IBW (Adjei et al 2003). Modelling has since been done that demonstrates functional dose equivalence between IBW dose and flat dose.

At the time of dose selection for this study, based on a data cut-off of 11 January 2017, a total of 157 patients had been treated with AZD9150 alone (100 patients) or in combination with durvalumab (57 patients, during Study D5660C00004 [NCT02499328]). During this study, a dose escalation of AZD9150 + durvalumab was initially conducted in 11 patients with mixed solid tumours. Durvalumab was administered at a dose of 20.0 mg/kg Q4W in combination with AZD9150 at starting doses of 2.0 and 3.0 mg/kg IBW given via 60-minute infusions of AZD9150 on Days -7, -5, and -3 of a 7-day lead-in period, followed by weekly dosing in these patients. This dose escalation established a recommended Phase II dose of durvalumab 20 mg/kg Q4W and AZD9150 3 mg/kg IBW weekly which is now being employed in head and neck cancer patients during an ongoing part of the D5660C00004 study. It is currently deemed suitable for further exploration in other tumour types except hepatocellular carcinoma. The most current dose rationale information can be found in the AZD9150 IB.

Preliminary safety data (based mainly on Common Terminology Criteria for Adverse Events [CTCAE] Grade ≥3 serious adverse event [SAE] reports from Study D5660C00004 and a pooled analysis of safety from across all ongoing studies) have shown that the most common Grade ≥3 SAEs were haematological (thrombocytopenia/platelet count decreased) and hepatic transaminase elevations.

A population PK model was developed for AZD9150 using PK data from Phase I/II studies (481464-CS1, D5660C00001 [NCT01839604], D5660C00004 [NCT02499328]) in patients with DLBCL, hepatocellular carcinoma (HCC) and SCCHN, respectively. A total of 123 patients received AZD9150 doses ranging from 1 to 4 mg/kg, with most of them on 3 mg/kg (n=70). Population PK analysis revealed IBW is not a significant covariate on the PK of AZD9150. The impact of IBW-based dose (3 mg/kg) versus flat dose (200 mg) was evaluated by comparing simulated steady state area under the curve (AUC) and maximum serum concentration (C_{max}) using the population PK model. A total of 1000 patients for each dosing regimen were simulated using body weight distribution of 30 to 100 kg. Simulation results demonstrate that IBW-based and flat dosing regimens (3 mg/kg versus 200 mg) yield similar median steady state AUC and C_{max} with slightly less overall between-patient

variability with the flat dosing regimen. Since a fixed dosing approach is preferred by the prescribing community and there is lack of influence of body weight on PK, a fixed dose of 200 mg will be used, instead of 3 mg/kg, as the starting dose of AZD9150 (Table 7).

Considering emerging PK data from ongoing studies, there is no evidence to indicate any ethnic sensitivity in Asian patients compared to Western patients.

4.4 End of study definition

Please refer to the core protocol.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, are not permitted.

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study in order to be assigned to a study cohort. Under no circumstances can there be exceptions to this rule. Patients who do not meet the entry requirements are screen failures; refer to Section 5.4 of the core protocol. 2 (HUDSON)

5.1 Inclusion criteria (Module 2-specific)

Refer to Section 5.1 of the core protocol for the inclusion criteria applicable to all modules in the study. There are no additional inclusion criteria for Module 2.

5.2 Exclusion criteria (Module 2-specific)

Patients must not enter Module 2 of the study if any of the following exclusion criteria apply. Refer to Section 5.2 of the core protocol for the exclusion criteria applicable to all modules in the study. Additional exclusion criteria applicable to Module 2 only are described below.

Prior/concomitant therapy

J-1 Prior exposure to AZD9150.

Prior/concurrent clinical study experience

J-2 Patients with a known hypersensitivity to AZD9150 or any of the excipients of the study drug.

For procedures for withdrawal of incorrectly enrolled patients see Section 7.3 of the core protocol.

5.3 Lifestyle restrictions

5.3.1 Restrictions applicable to durvalumab

Patients should not donate blood or blood components while participating in this study and through 90 days after receipt of the final dose of durvalumab or until alternate anticancer therapy is started.

Immunosuppressive medications including, but not limited to systemic corticosteroids at doses beyond 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumour necrosis factor alpha blockers are prohibited. Use of immunosuppressive medications for the management of study drug-related AEs and in patients with contrast allergies is acceptable. In addition, use of topical, inhaled and intranasal corticosteroids is permitted (see Table 4).

Live attenuated vaccines within 30 days of durvalumab dosing (ie, 30 days prior to the first dose, during treatment with durvalumab and for 180 days post-discontinuation of durvalumab). Inactivated viruses, such as those in the influenza vaccine, are permitted (see Table 4).

5.3.2 Restrictions applicable to AZD9150

None known.

5.4 Screen failures

Refer to Section 5.4 of the core protocol.

6. STUDY TREATMENTS

Study treatment is defined as any study drug(s) (including marketed product comparator and placebo) or medical device(s) intended to be administered to a study participant according to the study protocol. Study treatment in this Module 2 study refers to durvalumab and AZD9150.

6.1 Treatments administered

6.1.1 Study drugs

Table 2 Study treatments

	AZD9150	Durvalumab
Dosage formulation:	2 mL vial, 50 mg/mL concentrate for solution for infusion	Supplied as a vialed liquid solution containing 500 mg (nominal) durvalumab per vial. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine hydrochloride, 275 mM trehalose dihydrate, 0.02% (w/v) polysorbate 80, at pH 6.0. The nominal fill volume is 10.0 mL.
Route of administration	IV infusion	IV infusion
Dosing instructions:	AZD9150 200 mg every other day of a 1-week lead-in period followed by QW 1-hour infusion	Durvalumab 1500 mg via IV infusion Q4W ±2 days (fixed dosing for patients >30 kg body weight).
Packaging and labelling	Study treatment will be provided in vials. Labels will be prepared in accordance with GMP and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language, as required. AZD9150 will be provided with either single-panel labels or multi-language booklet labels. Specific dosing instructions will not be included on the label; the site must complete the "Patient Dispensing Card" with the details of the dosing instructions at the time of dispensing. The investigator's emergency contact details will not be on the label, but can be found in the informed consent and the 'Patient Dispensing Card'. For emergency purposes the patient must be in possession of the emergency contact details at all times.	Study drug will be provided in vials. Each vial will be labelled in accordance with GMP Annex 13 and per country regulatory requirement. Labels will be prepared in accordance with GMP and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language, as required. Durvalumab will be provided with either single-panel labels or multi-language booklet labels. The investigator's emergency contact details will not be on the label, but can be found in the informed consent and the 'Patient Emergency Card'. For emergency purposes the patient must be in possession of the emergency contact details at all times.
Provider	AstraZeneca	AstraZeneca. Commercially available 0.9% (w/v) saline or 5% (w/v) dextrose IV bags will be supplied by each site.

GMP Good Manufacturing Practice; IV=intravenous(ly); QW every week; Q4W every 4 weeks; w/v weight/volume

6.2 Preparation/handling/storage/accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study drugs received and any discrepancies are reported and resolved before use of the study drugs.

Only patients enrolled in the study may receive study drugs and only authorised site staff may supply or administer study drugs. All study drugs must be stored in a secure, environmentally

controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study drug accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study drugs are provided in the relevant appendices in the core protocol.

6.2.1 Durvalumab preparation and handling

Durvalumab will be supplied by AstraZeneca as a 500 mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine hydrochloride, 275 mM trehalose dihydrate, and 0.02% (weight/volume [w/v]) polysorbate 80; it has a pH of 6.0 and a density of 1.054 g/mL. The nominal fill volume is 10.0 mL.

Study drug vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. The vials should be kept in the original packaging until use to prevent prolonged light exposure.

The dose of durvalumab for administration must be prepared by the investigator's or site's designated study drug manager using aseptic technique. Total time from needle puncture of the durvalumab vial to the start of administration should not exceed 4 hours at room temperature or 24 hours at 2°C to 8°C (36°F to 46°F). Infusion solution must be allowed to equilibrate to room temperature prior to commencement of administration.

A dose of 1500 mg (for patients >30 kg body weight) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab concentration ranging from 1 to 15 mg/mL and delivered through an IV-administration set with a 0.2-µm or 0.22-µm filter. Add 30.0 mL (ie, 1500 mg) of durvalumab to an appropriately sized IV bag such that the final concentration is within 1 to 15 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

Weight-based dosing at 20 mg/kg (for patients ≤30 kg) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab concentration ranging from 1 to 15 mg/mL, and delivered through an IV administration set with a 0.2-µm or 0.22-µm filter. An example of a weight-based dose calculation is shown in Section 6.2.1.1.

Standard infusion time is one hour (±15 minutes), however if there are interruptions during infusion, the total allowed infusion time should not exceed 8 hours at room temperature.

If either preparation time or infusion time exceeds the time limits a new dose must be prepared from new vials. Durvalumab does not contain preservatives, and any unused portion must be discarded.

Do not co-administer other drugs through the same infusion line.

The IV line will be flushed with a volume of IV diluent equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered.

Durvalumab should be given at least 30 minutes after the patient has taken their AZD9150 dose (see Section 6.2.3). Patients will be monitored before, during, and after the first durvalumab infusion with assessment of vital signs at the times specified in the SoA (Table 1) and Section 8.2.3 of the core protocol. If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be at the investigator's discretion (suggested 30 minutes after each durvalumab infusion). For management of patients who experience an infusion reaction, please refer to the toxicity and management guidelines for infusion-related reactions at the following location: https://tmg.azirae.com. Module 2 (HUDSON)

Durvalumab (1500 mg) will be administered via IV infusion Q4W ± 2 days. Treatment with durvalumab will commence on Day 1 following confirmation of eligibility and will continue on a Q4W schedule until disease progression is confirmed.

6.2.1.1 Durvalumab weight-based calculation

If a patient's body weight falls ≤30 kg during the study, (s)he will be withdrawn from the study treatment unless (s)he derives some clinical benefit according to the treating physician. In this case, and following agreement between the treating physician and the Sponsor, the patient may continue treatment at a body-weight adapted dose of 20 mg/kg of durvalumab Q4W until the weight improves to >30 kg, at which point the patient should start receiving the fixed dosing of durvalumab 1500 mg Q4W:

1 Cohort dose: X mg/kg

2 Patient weight: Y kg

3 Dose for patient: XY mg = X (mg/kg) × Y (kg)

4 Dose to be added into infusion bag:

Dose (mL) = XY mg/50 (mg/mL) where 50 mg/mL is durvalumab nominal concentration.

The corresponding volume of durvalumab should be rounded to the nearest tenth mL (0.1 mL). Dose adjustments for each cycle are only needed for greater than 10% change in weight.

5 The number of vials required for dose preparation is the next greatest whole number of vials from the following formula:

Number of vials = Dose (mL) / 10.0 (mL/vial)

Example:

1 Cohort dose: 20 mg/kg
2 Patient weight: 30 kg
3 Dose for patient: 600 mg = 20 (mg/kg) × 30 (kg)
4 Dose to be added into infusion bag:

Dose (mL) = 600 mg / 50 (mg/mL) = 12.0 mL

5 The number of vials required for dose preparation:

Number of vials = 12.0 (mL) / 10.0 (mL/vial) = 2 vials

6.2.2 AZD9150 preparation and handling

AZD9150 will be supplied by AstraZeneca as a concentrate for solution for infusion. Each vial contains 50 mg/mL AZD9150 and the nominal fill volume is 2.0 mL (100 mg/vial). Study drug vials are stored at 2°C to 8°C (36°F to 46°F), protected from light, and must be used within the allocated expiry date.

6.2.2.1 Intravenous dose preparation and administration

Since the compatibility of AZD9150 with other IV medications and solutions, other than normal saline, is not known, the AZD9150 solution should **not** be infused through an IV line in which other solutions or medications are being administered.

When dosing in combination with durvalumab, the study drugs need to be given in the correct order as outlined in Section 6.2.3. The required time intervals between the administration of study drugs must be adhered to.

A dose of 200 mg will be administered using an IV bag containing 0.9% (w/v) saline and delivered through an IV-administration set. The drug solution for infusion should be clear, colourless and essentially free from visible particles. For the detailed dose preparation, refer to the Handling Instructions document provided by the sponsor.

The infusion line should be primed with normal saline prior to connecting it to the study drug IV bag. The entire contents of the IV bag should be administered at a constant rate over 1 hour. After the contents of the IV bag have been fully administered, the line should be flushed with a volume of normal saline equal to the priming volume of the infusion set used, or complete the infusion according to institutional policy to ensure the full dose is administered. Document if the infusion line was not flushed.

Total in-use storage time from needle puncture of the product vial to start of administration should not exceed 4 hours at room temperature or 24 hours at 2°C to 8°C (36°F to 46°F). It is not necessary to protect the diluted infusion from light during the period of preparation and administration. If in-use storage time exceeds these limits, a new dose must be prepared from new vials. The refrigerated infusion solutions in the prepared final bag should be equilibrated to room temperature for approximately 30 minutes prior to administration.

AZD9150 does not contain preservatives and any unused portion of concentrate in vial must be discarded.

6.2.3 Study drug administration

Administration of AZD9150

AZD9150 will be administered once per week, in a 4-week cycle with a 7-day lead-in (denoted Cycle 0) as shown in Table 3. AZD9150 should be administered as an IV infusion over approximately 60 minutes (± 10 minutes). During the 7-day lead-in period, AZD9150 will be administered as a loading dose on Days 1, 3 and 5 of Cycle 0. A window of +1 day per loading dose is allowed. Doses should not be given on consecutive days. Starting with Cycle 1, AZD9150 will be administered every week (QW) on Days 1, 8, 15, and 22 of each treatment cycle; doses have a ±2-day dosing window. If these dosing windows are missed, the AZD9150 dose should be skipped.

Administration of durvalumab

On the days that the 2 agents are given concurrently, the infusion of AZD9150 is to be completed at least 30 minutes before the start of the durvalumab infusion.

Following preparation of durvalumab (see Section 6.2.1), the entire contents of the IV bag should be administered as an IV infusion over approximately 60 minutes (±15 minutes).

Table 3 Treatment schedule, AZD9150 in combination with durvalumab

	7-day lead-in							Treatment Cycle 1 (and beyond)			
Cycle	**Cycle 0**							**Cycle 1 Week 1**	**Cycle 1 Week 2**	**Cycle 1 Week 3**	**Cycle 1 Week 4**
Day	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**1**	**8**	**15**	**22**
AZD9150 (IV)	x		x		x			x	x	x	x
Durvalumab (IV)								x			

IV=intravenous(ly)

Patients should continue to receive study treatment (ie, durvalumab in combination with AZD9150) until objective radiological disease progression as per Response Evaluation Criteria in Solid Tumours (RECIST 1.1), as long as, in the investigator's opinion, they are

benefiting from treatment and they do not meet any other discontinuation criteria. Disease progression should be confirmed by a subsequent scan (no earlier than 4 weeks later) in the absence of clinically significant deterioration as assessed by the investigator. All patients who have objective progression of disease will enter follow-up.

6.2.4 Storage

All study drugs should be kept in a secure place under appropriate storage conditions.

Durvalumab and AZD9150 are to be stored at the study centre in a secured facility with limited access and controlled temperature (2ºC to 8ºC). The temperature should be monitored on a daily basis and documented in the temperature monitoring log according to the study drug handling instructions.

The study drugs must be kept in the original outer container and under conditions specified on the labels.

In the following cases, the centre staff should not use affected study drug and should immediately contact AstraZeneca representative for further guidance:

- Temperature excursion upon receipt or during storage at the study site
- Damaged kit upon receipt
- Damaged vial/bottle

Damaged study drug should be documented according to the instructions provided by AstraZeneca representative. Storage instructions stated in the Investigator's Brochure, or the study drug Handling Instructions document, may be superseded by the label storage.

6.2.5 Accountability

The study drugs provided for this study should be used only as directed in the study protocol.

The study site staff will account for all study drugs received at the centre, for unused study drugs, and for appropriate destruction (according to local procedures). Certificates of delivery, destruction, and/or return should be signed.

The administration of all medications (including study drug) and details of treatment with study drug should be recorded in the appropriate sections of the electronic Case Report Form (eCRF).

Both durvalumab and AZD9150 will be administered IV at the study centre on treatment visits and within visit windows.

6.3 Measures to minimise bias: randomisation and blinding

This is an open-label study.

Recruitment into the biomarker non-matched arms will be conducted in a sequential manner.

If a patient withdraws from participation in the study, then his/her enrolment code cannot be reused. Withdrawn patients will not be replaced.

6.4 Treatment compliance

The administration of all study drugs should be recorded in the appropriate sections of the eCRF. Durvalumab and AZD9150 will be administered on site. Treatment compliance will be assured by reconciliation of site drug accountability logs.

Any change from the dosing schedule, does interruptions, dose reductions, dose discontinuations should be recorded in eCRF. Note: Dose reductions are not allowed for durvalumab without prior agreement with the study physician (see Section 6.6).

The Study Drug Storage Manager is responsible for managing the study drug from receipt by the study site until the destruction or return of all unused study drug.

Use of study drugs in doses in excess of that specified in the protocol is considered to be an overdose. Refer to Section 8.4.3 for procedures in case of overdose.

6.5 Concomitant therapy

Any medication or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the patient is receiving at the time of enrolment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Prohibited concomitant medications are described in Table 4. Please refer to Section 8.4.5 for guidance on management of study drug-related toxicities.

The use of concomitant medications must be recorded in the eCRF.

Table 4 Prohibited medications

Prohibited medication/class of drug:	
Unless stated otherwise, these medications are prohibited from the time that patients enter the main screening period until the last dose of study treatment. The pre-screen may be done whilst on prior therapy.	
Any investigational anticancer therapy other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment
Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment. (Note: concurrent use of hormones for non-cancer-related conditions [eg, insulin for diabetes and hormone replacement therapy] is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable [eg, by local surgery or radiotherapy]). Patients may receive treatment with bisphosphonates or RANKL inhibitors for the treatment of bone metastases
Immunosuppressive medications, including, but not limited to: systemic corticosteroids at doses exceeding 10 mg/day of prednisone or its equivalent, methotrexate, azathioprine, and tumour necrosis factor-α blockers	Should not be given concomitantly, or used for premedication prior to the infusions. The following are allowed exceptions: • Use of immunosuppressive medications for the management of study drug-related AEs • Short-term premedication for patients receiving combinations where the prescribing information for the agent requires the use of steroids for documented hypersensitivity reactions • Use in patients with contrast allergies • In addition, use of inhaled, topical, and intranasal corticosteroids is permitted. A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of non-immunotherapy related events experienced by the patient (eg, chronic obstructive pulmonary disease, radiation, nausea, etc).
Live attenuated vaccines	Prohibited from the time that patients enter the main screening period until 180 days after the last dose of study treatment.
Epidermal growth factor receptor (EGFR) Tyrosine kinase inhibitors (TKIs)	Should not be given concomitantly. Should be used with caution in the 90 days post last dose of durvalumab. Increased incidences of pneumonitis (with third generation EGFR TKIs) and increased incidence of transaminase increases (with 1st generation EGFR TKIs) has been reported when durvalumab have been given concomitantly.
Herbal and natural remedies which may have immune-modulating effects	Should not be given concomitantly unless agreed by the sponsor

AE adverse event

The use of herbal preparations/medications should be discouraged throughout the study. These herbal medications include, but are not limited to: St. John's Wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone, yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 7 days prior to first dose of study drug (3 weeks for St John's Wort). Use of these products, as well as use of all vitamins, nutritional supplements and all prescribed concomitant medications, must be recorded in the eCRF.

Other concomitant treatment

Medication other than that described above, which is considered necessary for the patient's safety and wellbeing, may be given at the discretion of the investigator and recorded in the appropriate sections of the eCRF.

6.5.1 Rescue and supportive medication

The study site will supply rescue medication and this will be procured locally. The sponsor will supply only if required by local regulations.

The use of rescue medications is allowable at any time during the study. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

Supportive medication, described in Table 5 may be given at the discretion of the investigator and recorded in the appropriate sections of the eCRF.

Table 5 Supportive medication

Supportive medication/class of drug:	Usage:
Concomitant medications or treatments (eg, acetaminophen or diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care, except for those medications identified as "prohibited," as listed above	To be administered as prescribed by the investigator
Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy to non-target lesions, etc])	Should be used, when necessary, for all patients
Inactivated viruses, such as those in the influenza vaccine	Permitted

6.5.2 Concomitant therapy with AZD9150

The PK evaluation of anti-sense molecules has been completed for numerous indications across multiple species from mouse to human. The PK properties of ASOs are largely independent of ASO sequence or drug target and thus similar for ASOs within the class. ASOs within this chemical class are rapidly cleared from plasma (distribution half-lives of 1 to 2 hours) and distribute broadly into tissue. ASOs are highly bound to plasma proteins (>90%). However, the protein binding sites of these hydrophilic ASOs differ from the binding sites of low molecular weight hydrophobic drugs, with few drug-drug interactions expected at clinically relevant concentrations. Further, ASOs are cleared from tissues by relatively slow nuclease hydrolysis and are not metabolised by cytochrome P450 enzymes.

Thus, ASOs are unlikely to interact metabolically with most small molecule drugs (Yu et al 2009).

Information on any treatment in the 4 weeks prior to starting study treatment and all concomitant treatments given during the study with reasons for the treatment should be recorded. If medically feasible, patients taking regular medication other than those excluded from this study should be maintained on it throughout the study period.

There are no known prohibited concomitant medications for AZD9150; but because AZD9150 is being studied in combination with durvalumab, there is a potential for and increased frequency of immune-mediated reactions. To date, however, no unexpected additional risks or toxicities have been identified.

6.6 Dose modification and discontinuation

For patients who weigh > 30 kg, the dose of durvalumab cannot be modified. If a patient's body weight falls ≤30 kg during the study, (s)he will be withdrawn from the study treatment unless (s)he derives some clinical benefit according to the treating physician. In this case, and following agreement between the treating physician and the Sponsor, the patient may continue treatment at a body-weight adapted dose of 20 mg/kg actual body weight.

Durvalumab dosing can be interrupted in the event of treatment-related toxicity. The maximum interruption or cycle delay that is permitted is 28 days. Any patient requiring a toxicity related dose delay of more than 28 days from the intended day of the next scheduled dose must be discontinued from the study unless there is approval from the Study Physician for the patient to continue. All toxicities will be graded according to Common Toxicity Criteria for Adverse Events (CTCAE) version 4.03. Dose reductions are not permitted without prior agreement with the study physician. Please refer to the toxicity management guidelines for durvalumab at the following location: URL: https://tmg.azirae.com.

For dose modifications of AZD9150, see Section 8.4.5.

6.7 Treatment after the end of the study

Patients are permitted to either receive standard of care therapy, or to continue to receive study treatment following the end of the study if, in the opinion of the investigator, they are continuing to receive benefit from treatment. After discontinuation of study treatment, the investigator will be at liberty to define further most appropriate anti-cancer treatment. Subsequent anti-cancer treatment is expected to be initiated following the cancer recurrence or development of a new cancer. Information on subsequent anti-cancer therapies should be recorded on the clinical database.

7. DISCONTINUATION OF TREATMENT AND PATIENT WITHDRAWAL

Please refer to Section 7 in the core protocol. Guidance on re-allocation to a second treatment cohort is provided in Section 7.4 of the core protocol.

Study procedures and their timing for patients re-allocated to a second study treatment are summarised in the re-allocation SoA (Table 6).

Table 6 Schedule of Activities – re-allocated to second on-treatment period (Module 2)

	C0 (Table 3)			C1 (28 days) Weeks 1-4				C2 (28 days) Weeks 5-8				C3 – etc All cycles 28 days				Study drug disc. (28 days after study drug disc.)	Safety follow-up (90 days after study drug disc.)	Survival follow-up	Notes
Week	**One week lead-in**			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**				
Day of cycle	**1**	**3**	**5**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**				
Window (days)	**+1[a]**			**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±7**	**±7**	**±7**	
Study procedures																			
Informed consent	X																		Section 5.2.1 (core protocol). Patient must consent to new treatment. Will be performed within 28 days before dosing.
Eligibility criteria for re-allocation[b]	X																		Patients must meet eligibility criteria in the core CSP (see Table 1) and in this module
Physical examination	X			X		X		X		X		X				X			Section 8.2.2 (core protocol)
Vital signs[c]	X			X		X		X		X		X				X			Section 8.2.3 (core protocol)
ECG				X	As clinically indicated														Section 8.2.4 (core protocol)
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			Section 6.5

Table 6 Schedule of Activities – re-allocated to second on-treatment period (Module 2)

	C0 (Table 3)			C1 (28 days) Weeks 1-4				C2 (28 days) Weeks 5-8				C3 – etc All cycles 28 days				Study drug disc. (28 days after study drug disc.)	Safety follow-up (90 days after study drug disc.)	Survival follow-up	Notes
Week	**One week lead-in**			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**				
Day of cycle	**1**	**3**	**5**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**				
Window (days)	**+1[a]**			**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±7**	**±7**	**±7**	
Laboratory assessments																			
Clinical chemistry	X			X		X		X		X		X				X			Section 8.2.1 (core protocol). If screening laboratory assessments are performed within 3 days prior to C0D1 they do not need to be repeated at C0D1.
Haematology	X			X		X		X		X		X				X			
APTT and INR	As clinically indicated																		
TSH, free T_3, and free T_4	X			X		X		X		X		X				X			Section 8.2.1 (core protocol)
Urinalysis					As clinically indicated														Section 8.2.1 (core protocol)
Pregnancy test	X			X				X				X				X			Section 8.2.1.2 (core protocol)
AE/SAE assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Section 8.3 (core protocol)
Study drug administration																			
Durvalumab				X				X				X							Section 6.2.3
AZD9150	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				Section 6.2.3
Drug accountability	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			Section 6.2.5

Table 6 Schedule of Activities – re-allocated to second on-treatment period (Module 2)

	C0 (Table 3)			C1 (28 days) Weeks 1-4				C2 (28 days) Weeks 5-8				C3 – etc All cycles 28 days				Study drug disc. (28 days after study drug disc.)	Safety follow-up (90 days after study drug disc.)	Survival follow-up	Notes
Week	**One week lead-in**			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**				
Day of cycle	**1**	**3**	**5**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**				
Window (days)	**+1[a]**			**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±7**	**±7**	**±7**	
Other assessments																			
Subsequent cancer therapy																	X	X	These assessments are repeated here from Table 1. Patients will be followed for survival from the original treatment cohort. These are not additional assessments for re allocation, they are only repeated here for completeness.
Survival status																		X	

[a] Every effort should be made to minimise the time between allocation to treatment and starting treatment. Note, if main screening assessments have been performed within 3 days prior to C0D1, then assessments do not need to be performed on C1D1 or C0D1 pre-dose.

[b] Eligibility criteria in core CSP and in this module apply

[c] Vital signs to be taken prior to AZD9150 infusion and as per core CSP section 8.2.3.

Note, if main screening assessments have been performed within 3 days prior to C0D1, then assessments do not need to be performed on C1D1 or C0D1 pre-dose.

AE adverse event; APTT activated partial thromboplastin time; C cycle; ECG electrocardiogram; INR international normalised ratio; SAE serious adverse event; TSH thyroid-stimulating hormone; T_3 triiodothyronine; T_4 thyroxine.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timings are summarised in the SoA (Table 1). Study procedures and their timing for patients re-allocated to a second study treatment are summarised in the re-allocation SoA (Table 6).

8.1 Efficacy assessments

Please refer to the core protocol.

8.2 Safety assessments

8.2.1 Clinical safety laboratory assessments

Please refer to core protocol. Please note that haptoglobin and fibrinogen are to be measured approximately monthly for patients treated with durvalumab in combination with AZD9150 in Module 2. More frequent assessments may be performed if clinically indicated.

8.2.1.1 Coagulation

Please refer to core protocol.

8.2.1.2 Other safety assessments

Please refer to core protocol.

8.2.1.3 Pneumonitis (interstitial lung disease) investigation

The following assessments, and additional assessments if required, will be performed to enhance the investigation and diagnosis of potential cases of pneumonitis. The results of the assessment will be collected.

- Physical examination; Signs and symptoms (cough, shortness of breath and pyrexia, etc) including auscultation for lung field will be assessed.
- SpO_2; Saturation of peripheral oxygen (SpO_2)
- Other items; When pneumonitis (interstitial lung disease [ILD]) is suspected during study treatment, the following markers should be measured where possible:
  - ILD Markers (KL-6, SP-D) and β-D-glucan
  - Tumour markers: Particular tumour markers which are related to disease progression.

8.2.2 Physical examinations

Please refer to core protocol.

8.2.3 Vital signs

Please refer to core protocol. An additional vital sign measurement is required on day 1 of each cycle, from cycle 1 onwards. This measurement will be taken prior to AZD9150 infusion. Post-infusion vital signs to be taken following the instructions given for durvalumab.

Vital signs will be collected at every designated visit pre-dose after an adequate rest period, 30 minutes after start of infusion, and 15 minutes after the end of each infusion for AZD9150 and durvalumab. In addition to pre-dose readings, blood pressure readings will be taken to coincide with PK sampling (blood pressure taken ±10 minutes from the designated times).

8.2.4 Electrocardiograms

Please refer to core protocol

8.2.5 Performance status

Please refer to core protocol

8.3 Collection of adverse events

Please refer to the core protocol.

8.4 Safety reporting and medical management

8.4.1 Reporting of serious adverse events

Please refer to the core protocol.

8.4.2 Pregnancy

Please refer to the core protocol.

8.4.3 Overdose

A dose of AZD9150 in excess of that specified according to the protocol will constitute an overdose. There is currently no known antidote to AZD9150, and the treatment of overdose should be supportive for the underlying symptoms. To date, no patient treated with AZD9150 has experienced an overdose that was associated with an AE.

Please refer to Section 8.4.3 of the core protocol.

8.4.4 Medication error

Please refer to Section 8.4.4 in the core protocol.

8.4.5 Management of study drug-related toxicities

8.4.5.1 Management of durvalumab-related toxicities

Please refer to the toxicity management guidelines for durvalumab at the following location: URL: https://tmg.azirae.com.

8.4.5.2 Management of AZD9150-related toxicities

Patients receiving the combination of AZD9150 plus durvalumab may report AEs that are known to be associated with AZD9150 alone. Management guidelines for such AEs (eg, thrombocytopenia and elevated liver enzymes) are provided below.

Management of AZD9150-related toxicities in general

If a patient has a clinically significant and/or unacceptable toxicity, not attributable to the disease or disease-related processes under investigation, where the investigator considers the AE of concern to be specifically associated with AZD9150, dosing will be interrupted (for a period of up to 21 days) and/or the dose reduced and supportive therapy administered as required. The maximum interruption or cycle delay that is permitted is 21 days. Any patient requiring a toxicity related dose delay of more than 21 days from the intended day of the next scheduled dose must be discontinued from the study unless there is approval from the Study Physician for the patient to continue.

Please refer to Table 7, Table 8 and Table 9 for further details. Once reduced, the dose of AZD9150 cannot be re-escalated.

Ongoing clinical benefit is best judged by the treating physician and in discussion with the sponsor/medical monitor on a case by case basis. If, in the estimation of the investigator, with the concurrence of the medical monitor, a patient is deemed to be deriving clinical benefit, the specified treatment may be resumed. This estimation will be based on criteria including but not limited to disease-related symptoms, performance status, physical examination, and (as required) additional appropriate imaging studies

In order to initiate a new cycle of therapy with durvalumab and AZD9150, the patient must have a platelet count ≥50 x 10^9/L and no drug-related non-haematological Grade ≥3 toxicity on Day 1.

If these criteria are not met (but the patient derives clinical benefit), the entire cycle with all drugs is to be delayed to a maximum of 4 treatment weeks (28 days). Treatment may only be restarted once the results of repeat assessments indicate that these criteria have been met.

Substantial acute toxicities should be managed as medically indicated and with temporary suspension of IP, as appropriate.

Dose reductions or holds and initiation of supportive care are allowed as clinically indicated by the treating physician. In general, for each patient, a maximum of 2 dose reductions of AZD9150 will be allowed, however, exceptions to this rule may be discussed with the AstraZeneca Study Physician on a case-by-case basis. The AZD9150 dose level modifications are presented in Table 7.

Table 7 Recommended dose reductions for AZD9150 for management of treatment-emergent toxicities

Dose level	AZD9150 dose
Starting Dose AZD9150[a]	200 mg QW
-1 Dose Level	200 mg Q2W
-2 Dose Level	150 mg Q2W

[a] Prior to the first cycle of combination dosing, AZD9150 is given on Days -7, -5 and -3 of a 7-day lead-in period.
QW=Every week; Q2W=Every 2 weeks.

In general, if a patient experiences a Grade 1/Grade 2 haematological or non-haematological toxicity, no dose modification of AZD9150 is required.

If a patient experiences a Grade 3 or Grade 4 toxicity, not attributable to the disease or disease-related processes under investigation, dosing of AZD9150 will be interrupted and/or the dose reduced (see Table 7) and supportive therapy administered as required.

If the toxicity resolves or reverts to CTCAE Grade ≤2 within 3 treatment weeks and the patient is showing clinical benefit, treatment with AZD9150 may be restarted.

If the toxicity does not resolve to CTCAE Grade ≤2 after 3 weeks off treatment and the patient does not show clinical benefit, then the patient should be withdrawn from the study and observed until resolution of the toxicity. For an intermittent dosing break, the maximum number of days allowed is 21 days.

If the toxicity does not resolve to CTCAE Grade ≤2 after 3 weeks off treatment but the patient does show clinical benefit, treatment with AZD9150 may be restarted after discussion with the medical monitor.

The investigator may make dose modifications if he/she considers these are related to the combination therapy, otherwise please refer to Section 8.4.6.

Management of AZD9150-associated haematological toxicities

In order to initiate a new cycle of therapy with AZD9150, the patient must have a platelet count ≥50 x 10^9/L and no drug-related non-haematological Grade ≥3 toxicity on Day 1. Generally, Grade 1 or 2 haematological toxicities do not require AZD9150 dose reductions and should be managed as medically indicated (with or without short dose interruptions) by

the treating physician; however, the investigator should alert the study physician as soon as possible, in the event that Grade 1 or 2 decreases in platelet count are observed, and should consider early referral to a haematology specialist. Platelets may be transfused at the discretion of the investigator.

Dose modifications of AZD9150 for Grade ≥3 haematological toxicity (and other toxicities, excluding liver function tests) should be managed as shown in Table 8.

Table 8 AZD9150 dose modifications for toxicity (excluding liver function tests)

Toxicity	Recovery	Re-dosing	Notes
Grade 3	G2[a] ≤21 days	Restart at dose level -1 (200 mg Q2W)	If second dose interruption, decrease to dose level -2 (150 mg Q2W)
	G2[a] >21 days	Discontinue study drug treatment	
Grade 4	G2[a] ≤21 days	Restart at dose level -2 (150 mg Q2W)	If second grade 4 toxicity, discontinue study drug treatment
	G2[a] >21 days	Discontinue study drug treatment	

[a] Patients starting with an abnormal baseline may restart when the laboratory value/AE returns to pre-treatment status. If thrombocytopenia is accompanied by bleeding, discontinue study drug treatment.
G grade; Q2W every 2 weeks.

If in the clinical judgment of the investigator, the thrombocytopenia events with patients on AZD9150 monotherapy or in combination with durvalumab need to be managed in a way different from that proposed in Table 8, it will warrant discussion with the Study Physician and approval/waiver on the alternate management.

Also, a single case of Serious Unexpected Serious Adverse Reaction (SUSAR) considered by the investigator as a possibly-related thrombotic microangiopathy occurred in a patient dosed at 4 mg/kg of AZD9150 (described in detail in the Investigator's Brochure for AZD9150). It is noted here only due to the serious nature of the event; however, no other cases of thrombotic microangiopathy or related thrombotic events have been identified other patients. According to the sponsor, the event was thought to be most likely associated with the patient's underlying advanced DLBCL, but a contribution of AZD9150 could not be ruled out due to the temporal relationship to dosing. No routine monitoring beyond the current baseline haematological parameters is currently regarded as necessary.

Management of non-haematological AZD9150-associated toxicities

Recommendations for evaluation and treatment of liver function test abnormalities

Liver enzyme elevation is an identified risk of AZD9150 administration, determined from clinical experience in the liver-compromised hepatocellular carcinoma patients and other populations studied so far.

Evidence of abnormal liver function should be monitored as per the protocol guidelines. Increased levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), or serum bilirubin should trigger an investigation of the cause, which may include viral infection or disease progression with liver infiltration. The investigator should consider whether the abnormal liver function meets the criteria for expedited reporting; please refer to Appendix E in the core protocol (actions required in case of increases in liver biochemistry and evaluation of Hy's Law).

If Grade ≥3 hepatic abnormalities are observed while the patient is on study, follow dose modification advice shown in Table 9.

Table 9 AZD9150 dose modifications for elevations in liver function tests

Toxicity	Recovery	Re-dosing	Notes
Grade 3	G1[a] ≤21 days	Restart at dose level -1 (200 mg Q2W)	If second dose interruption, decrease to dose level -2 (150 mg Q2W)
	G1[a] >21 days	Discontinue study drug treatment	
Grade 4 – and assessed by the investigator as related to study treatment		Discontinue study drug treatment	

[a] Patients starting with an abnormal baseline may restart when the lab/AE returns to pre-treatment status.
G grade; Q2W every 2 weeks.

8.4.6 Durvalumab and AZD9150 combination

The safety profiles of durvalumab and AZD9150 have been subject to ongoing internal evaluation by AstraZeneca. On a theoretical basis, as both drugs may cause AST/ALT increases, albeit by different mechanisms of action, there is potential for an increase in severity and frequency of AST and ALT increase when durvalumab is given in combination with AZD9150. There is no additional risk of increase in myelosuppressive AEs observed with AZD9150 when given in combination with durvalumab. Hence, patients will be closely monitored for all infusion-related adverse events (irAEs), liver toxicities, and myelosuppression in the current study.

In the event of toxicity with the combination treatment (AZD9150 plus durvalumab) that cannot be managed by supportive measures alone, consider stopping or reducing the dose of AZD9150. The recommended dose reductions for AZD9150 are presented in Table 7.

8.4.6.1 Toxicity management guidelines for combination therapy (durvalumab plus AZD9150)

Specific management guidelines for AEs that are associated with durvalumab and/or AZD9150, toxicity should be managed according to the guidelines provided above for AZD9150 (Section 8.4.5) and the toxicity management guidelines for durvalumab at the following location: URL: https://tmg.azirae.com.

The following general guidance in the core protocol should be followed for management of other toxicities:

- Treat each of the toxicities with maximum supportive care (including slowing/interrupting /omitting the agent suspected of causing the toxicity where required).
- If durvalumab is discontinued for more than 28 days or AZD9150 treatment is discontinued for more than 21 days, the patient should permanently discontinue study treatment. If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of durvalumab ± AZD9150 along with appropriate continuing supportive care.
- All dose modifications should be documented with clear reasoning and documentation of the approach taken.

In addition, the following are recommended:

- Patient evaluation to identify any alternative aetiology.
- In the absence of a clear alternative aetiology, all events of an inflammatory nature should be considered to be immune-related.
- Symptomatic and topical therapy should be considered for low-grade events.
- For persistent (greater than 3 to 5 days) low-grade (Grade 2), or severe (Grade ≥3) events promptly start oral prednisone 1 to 2 mg/kg/day or IV equivalent.
- If symptoms recur or worsen during corticosteroid tapering (≥4 weeks of taper), increase the corticosteroid dose (prednisone dose [eg, up to 2 to 4 mg/kg/day or IV equivalent]) until stabilisation or improvement of symptoms, then resume corticosteroid tapering at a slower rate.
- More potent immunosuppressives (refer to individual sections of the immune-related AE for specific type of immunosuppressive) should be considered for events not responding to systemic steroids.
- Discontinuation of study drug is not mandated for Grade 3/Grade 4 inflammatory reactions attributed to local tumour response (eg, inflammatory reaction at sites of metastatic disease, lymph nodes, etc). Continuation of study drug in this situation should

be based upon a benefit/risk analysis for that patient and be discussed with the Study Physician.

- If the CTCAE Grade 3 toxicity resolves or reverts to Grade ≤2 within 3 treatment weeks and the patient is showing clinical benefit per the investigator, study treatment with AZD9150 and durvalumab may be restarted per the guidelines in Table 8 and Table 9.

For all CTCAE Grade 4 toxicities, permanently discontinue AZD9150 and durvalumab.

8.4.7 Adverse events of special interest

Adverse events of special interest (AESIs) are of scientific and medical interest specific to further understanding of the study drug profile and may require close monitoring. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterise and understand them in association with the use of this study drug.

The AESIs for durvalumab are summarized in core protocol Section 8.3.12.

There are no AESIs for AZD9150.

At present, no reporting of AESIs for patients receiving AZD9150 alone is deemed necessary. Any AZD9150-specific AESIs will be defined prior to database lock.

8.5 Pharmacokinetics

Please refer to the core protocol.

8.6 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7 Genetics

Please refer to the core protocol.

8.8 Biomarkers

Please refer to the core protocol.

8.9 Medical Resource Utilisation and Health Economics

Medical Resource Utilisation and Health Economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

Please refer to the core protocol.

10. REFERENCES

Adjei et al 2003
Adjei AA, Dy GK, Erlichman C, Reid JM, Sloan JA, Pitot HC, et al. A phase I trial of ISIS 2503, an antisense inhibitor of H-ras, in combination with gemcitabine in patients with advanced cancer. Clin Cancer Res. 2003;9(1):115-23.

Alvarez et al 2005
Alvarez JV, Febbo PG, Ramaswamy S, Loda M, Richardson A, Frank DA. Identification of a genetic signature of activated signal transducer and activator of transcription 3 in human tumors. Cancer Res 2005;65:5054–62.

Al Zaid Siddiquee and Turkson 2008
Al Zaid Siddiquee K and Turkson J. STAT3 as a target for inducing apoptosis in solid and hematological tumors. Cell Res 2008;2:254–67.

Avalle et al 2012
Avalle L, Pensa S, Regis G, Novelli F, Poli V. STAT1 and STAT3 in tumorigenesis. JAK-STAT. 2012;1:2,65-72.

Ayers et al 2015
Ayers M, Lunceford J, Nebozhyn M, Murphy E, Loboda A, Albright A, et al. Relationship between immune gene signatures and clinical response to PD-1 blockade with pembrolizumab (MK-3475) in patients with advanced solid tumors. Journal for ImmunoTherapy of Cancer. 2015; 3(2):P80.

Garassino et al 2017
Garassino M, Vansteenkiste J, Joo-Hang Kim, Hervé Léna, Mazières J, Powderly J, et al. PL04a.03: Durvalumab in ≥3rd-Line Locally Advanced or Metastatic, EGFR/ALK Wild-Type NSCLC: Results from the Phase 2 ATLANTIC Study. J Thor Onc 2017;12:S10–S11.

Hong et al 2015
Hong D, Kurzrock R, Kim Y, Woessner R, Younes A, Nemunaitis J, et al. AZD9150, a next-generation antisense oligonucleotide inhibitor of STAT3 with early evidence of clinical activity in lymphoma and lung cancer. Sci Transl Med. 2015;7,314ra185.

Kortylewski et al 2005
Kortylewski M, Kujawski M, Wang T, Wei S, Zhang S, Pilon-Thomas S, et al. Inhibiting Stat3 signaling in the hematopoietic system elicits multicomponent antitumor immunity. Nature Medicine. 2005;11(12):1314-21.

Kortylewski and Yu 2008
Kortylewski M, Yu H. Role of Stat3 in suppressing anti-tumor immunity. Current Opinion in Immunology 2008;20:228–33.

Kordylewski et al 2009
Kortylewski M, Xin H, Kujawski M, Lee H, Liu Y, Harris T, et al. Regulation of the IL-23 and IL-12 balance by Stat3 signaling in the tumor microenvironment. Cancer Cell 2009;15:114–23.

McCoon et al 2015
McCoon P, Woessner R, Grosskurth S, Womack C, Yamashita M, Hung G, et al. Clinical and pre-clinical evidence of an immune modulating role for STAT3-targeting ASO AZD9150 and potential to enhance clinical responses to anti-PDL1 therapy. AACR Annual Meeting 2015, Clinical Trials of Novel Therapeutics Session. 20 April 2015.

Narwal et al 2013
Narwal R, Roskos LK, Robbie GJ. Population Pharmacokinetics of Sifalimumab, an Investigational Anti-Interferonalpha Monoclonal Antibody, in Systemic Lupus Erythematosus. Clin Pharmacokinet 2013;52:1017–27.

Ng et al 2006
Ng CM, Lum BL, Gimenez V, Kelsey S, Allison D. Rationale for fixed dosing of pertuzumab in cancer patients based on population pharmacokinetic analysis. Pharm Res 2006;23(6):1275–84.

Ribas et al. 2015
Ribas A, Robert C, Hodi S, Wolchok D, Joshua A, Hwu W et al. Association of response to programmed death receptor 1 (PD-1) blockade with pembrolizumab (MK-3475) with an interferon-inflammatory immune gene signature. DOI: 10.1200/jco.2015.33.15_suppl.3001 Journal of Clinical Oncology 33, no. 15_suppl (May 2015) 3001-3001.

Villerino et al 2017
Villerino AV, Kanno Y, O'Shea JJ. Mechanisms and consequences of Jak–STAT signaling in the immune system. Nature Immunology. 2017;18(4):374-84.

Wang et al 2004
Wang T, Niu G, Kortylewski M, Burdelya L, Shain K, Zhang S, et al. Regulation of the innate and adaptive immune responses by Stat-3 signaling in tumor cells. Nature Medicine. 2004;10(1):48-54.

Wang et al 2009
Wang DD, Zhang S, Zhao H, Men AY, Parivar K. Fixed dosing versus body size based dosing of monoclonal antibodies in adult clinical trials. J Clin Pharmacol 2009;49(9):1012–24.

Woessner et al. 2016
Woessner R, McCoon P, Grosskurth S, Deng N, Bell K, Collins M, et al. Response to immune checkpoint modulators is enhanced by the addition of STAT3 antisense treatment in

preclinical tumor models. Keystone Symposium on Cytokine JAK-STAT Signaling in Immunity and Disease, January 14, 2016

Woessner et al. 2017
Woessner R, Sah V, McCoon P, Grosskurth S, Deng N, DuPont R, et al. Inhibition of STAT3 by Antisense Oligonucleotide Treatment Decreases the Immune Suppressive Tumor Microenvironment in Syngeneic and GEM Tumor Models. Cancer Res 2017;77(13 Suppl):Abstract Number 3684.

Yu et al 2007
Yu H, Kortylewski M, Pardoll D. Crosstalk between cancer and immune cells: role of STAT3 in the tumour microenvironment. Nat Rev Immunol 2007;7(1):41–51.

Yu et al 2009
Yu RZ, Lemonidis KM, Graham MJ, Matson JE. Cross-species comparison of in vivo PK/PD relationships for second generation antisense oligonucleotides targeting apolipoprotein B-100. Biochem Pharmacol 2009;77:910–919.

Zhang et al 2012
Zhang S, Shi R, Li C, Parivar K, Wang DD. Fixed dosing versus body size-based dosing of therapeutic peptides and proteins in adults. J Clin Pharmacol 2012;52(1):18–28.

Clinical Study Protocol

Drug Substance	Umbrella study
Study Code	D6185C00001 (HUDSON)
Version	14.0
Date	09 October 2024

Appendix K

Module 3: Durvalumab plus AZD6738

An Open-Label, Multi-Drug, Biomarker-Directed, Multi-Centre Phase II Umbrella Study in Patients with Non-Small Cell Lung Cancer, who Progressed on an Anti-PD-1/PD-L1 Containing Therapy (HUDSON)

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

Regulatory Agency Identification Numbers:

EudraCT number: 2017-002208-28

EU CT number: 2023-509004-15-00

IND number: 138050

VERSION HISTORY

Version 14.0, 09 October 2024
Key amendments and rationale for changes: **Section 2.2.2.2, AZD6738 data:** CCI [redacted] **Table 2, study drug:** removed reference to Annex 13. **Section 6.5.2, effect of AZD6738 on other drugs; Section 11, AZD6738 drug-drug interactions:** Updated to describe AZD6738 as an inducer of CYPCCI CYPCCI and CYPCCI and a weak inhibitor of CYPCCI and CYPCCI **Section 8.4.1, reporting of serious adverse events:** addition of text relating to the reporting of MDS and/or AML during follow-up. **Section 8.4.5.2, management of AZD6738-related toxicities:** • Guidance was added for patients who experience suspected MDS/AML. • New sub-section was added to describe actions to be taken if a patient displays suspected indications of MDS and/or AML. **Table 9, drugs known to be inhibitors and inducers of CYPCC:** Ceralasertib was added as a potent CYPCC inducer. Minor text clarifications were also made.

Version 13.0, 14 December 2023
Key amendments and rationale for changes: **Front page:** EU CT number has been added in line with the core CSP. **Section 6.1.1, study drugs:** Text regarding 'Packaging and Labelling' updated to remove the information that labels will fulfil GMP Annex 13 requirements for labelling, as this Annex has been replaced.

Version 12.0, 01 March 2023

Key amendments and rationale for changes:

Table 1, schedule of activities:

- Addition of a footnote to clarify the windows allowed for the administration of the study drugs.
- The visit in which flow cytometry samples are to be collected was updated in the footnote.

Section 2.2.1.2, durvalumab data: References for published studies were added.

Section 2.2.2.1, overview of AZD6738; Section 2.2.2.2 AZD6738 data: Updated in line with the new AZD6738 IB Edition 11.

Section 4.3.1, justification for durvalumab dose: Added a cross-reference to the durvalumab IB for updates on data from ongoing studies.

Table 2, study drugs; Section 6.2.1 Durvalumab preparation and handling: The window for durvalumab infusion administration was clarified.

Section 6.2, preparation/handling/storage/accountability: Added a reference to the Pharmacy Manual.

Section 6.5.2, effect of AZD6738 on other drugs: Added cross-reference to Section 11 for details on AZD6738 drug-drug interactions.

Section 6.6, dose modification and discontinuation; 8.4.5.2 Management of AZD6738-related toxicities: Updated to clarify the procedures to follow after a study treatment dose delay.

Section 10, references: The list of references was updated in line with the citation in the text.

Section 11, AZD6738 drug-drug interactions: Section added, in line with Modules 8, 9, and 11.

In addition, minor typographical errors have been corrected throughout where applicable.

Version 11.0, 16 August 2022

Key amendments and rationale for changes:

Table 1, schedule of activities:

- Addition of lymphocyte and neutrophil counts to the haematology footnote to clarify these will be recorded for patients dosed in the expanded cohorts as part of the routine white blood cell count for safety assessment and collected retrospectively for patients already enrolled in the expanded cohorts.
- Removal of Day 22 (Cycles 1 and 2) CCI sample collection and footnote added to clarify timing of sample collection. This change is made to align with other AstraZeneca projects.
- Addition of footnote for flow cytometry samples to clarify that if a sample is not collected at the screening (baseline) visit, there is no requirement to collect further samples for analysis at subsequent study visits as analysis requires a baseline result for comparison.
- Addition of footnote to state that on-treatment biopsy is not required if a fresh tumour sample is not collected at pre-screening as analysis requires a baseline result for comparison (ie, from the pre-screening sample).

Section 6.2.3, storage: Text is updated to clarify monitoring of temperature refers to study drug (durvalumab) storage.

Version 10.0, 12 April 2022

Key amendments and rationale for changes:

Table 1, schedule of activities:

- Addition of table footnote to clarify from implementation of protocol v10.0, optional treatment re-allocation of patients to a different treatment cohort is no longer applicable.
- Addition of footnote to clarify the activities for patients continuing on study treatment after the data cut-off for the module clinical study report.
- Addition of footnote to clarify eosinophil and monocyte counts will be recorded for patients dosed in expanded cohorts and collected retrospectively for patients already enrolled in expanded cohorts.
- Addition of footnote to clarify additional safety assessment will take place on Day 22 from Cycle 3 onwards if a patient has an event of thrombocytopenia, anaemia and/or neutropenia that is ≥ Grade 3 during the first 2 cycles. To align with Modules 8 and 9.
- Additional time point added at Cycle 0, Day 1 for aPTT, INR and urinalysis to detect the possibility of bleeding.

- Blood sample for flow cytometry label clarified.
- Additional blood sample at Cycle 2 Day 22 visit included for the following assessments: Circulating soluble factors, gene expression, immunophenotyping, and TCR immuno-sequencing. To monitor pharmacodynamic activity of AZD6738 and durvalumab.
- Additional blood sample at study drug discontinuation visit included for the following assessments: Immunophenotyping and TCR immuno-sequencing. To evaluate immune phenotype status at discontinuation of study drug.

Figure 1, study design: Footnote added to clarify survival follow-up of screen failures and optional treatment re-allocation to a second treatment cohort are no longer required from implementation of protocol v10.0.

Section 2.2 background: Reference to approval of durvalumab for the treatment of urothelial carcinoma in the US removed due to voluntary withdrawal of this indication in this country. Text also added to clarify the weight-based regimen (10 mg/kg every 2 weeks) is approved for urothelial carcinoma.

Section 2.2.1.2, durvalumab data: Number of patients treated with durvalumab was updated to align with the durvalumab IB Edition 17.

Section 2.2.2.2, AZD6738 data: Text updated to align with AZD6738 IB Edition 10.

Section 2.2.3, Durvalumab and AZD6738 in combination: Text added for the recommended Phase II dose from Study D553000004 Module 3.

Section 4.3.2, justification for AZD6738 dose: Additional safety data for the AZD6738 plus durvalumab dosing schedule included per the AZD6738 IB Edition 10 CCI [redacted]

Section 5.3.1, restrictions applicable to durvalumab; Table 5, supportive medication: Text added to provide guidance for the use and timing of authorised and approved COVID-19 vaccines, to align with the COVID-19 vaccination guidance letter (dated 24 February 2021) provided to sites. Text for live attenuated vaccines also amended for clarification.

Table 5, supportive medication: Text added to clarify when AZD6738 treatment should be discontinued and restarted before and after a patient undergoes palliative radiation treatment to align with the Ceralasertib Project Specific Safety Requirements v14.

Section 6.5.2, effect of AZD6738 on other drugs; Section 6.6 and Table 6, AZD6738 dose modifications for toxicity management; Table 8, dose interruption and stopping criteria: Text updated per the Ceralasertib Project Specific Safety Requirements v14.

Section 6.6, dose modification and discontinuation:

- Text describing dose interruption or cycle delay clarified to align with similar text in Module 9; text (and cross reference to Section 7.1.1 of the core protocol) added to clarify that a patient may continue on monotherapy if the other treatment is permanently stopped.
- Text added to describe when study treatment should be stopped in relation to planned surgery, to align with Module 8 and the Ceralasertib Project Specific Safety Requirements v14.

Section 7, discontinuation of treatment and patient withdrawal: Sentence added to clarify as of implementation of protocol v10.0, re-allocation of patients to a different treatment cohort is no longer applicable.

Section 8.2.1, clinical safety laboratory assessments: Text added for addition of eosinophil and monocyte counts to be performed as part of the white blood cell count safety assessment for patients in the expanded cohorts.

Section 8.6, pharmacodynamics: Text updated to clarify pharmacodynamic parameters will be evaluated in the study and a cross reference to Section 8.6 of the core protocol added.

In addition, minor typographical errors have been corrected throughout where applicable.

Version 9.0, 14 May 2021

Key amendments and rationale for changes:

The version number of this module has been revised in line with the other modules in the HUDSON study; however, no changes have been made to this module.

Version 8.0, 11 September 2020

Key amendments and rationale for changes:

Removal of web link to the durvalumab toxicity management guidelines as this website has been decommissioned. The toxicity management guidelines will instead be provided to sites: Section 6.2.1, Section 6.6, and Section 8.4.5.1.

Section 8.4.5.2 Management of AZD6738-related Toxicities: Table and text updated based on updated safety information.

Version 7.0, 21 May 2020

Key amendments and rationale for changes:

Section 2.2 Background: Update to the registered use and approvals for durvalumab.

Section 2.2.2.2 AZD6738 and **Section 2.2.3:** Updates to align with AZD6738 IB Edition 8.

Figure 2 (study flow diagram): this figure has been removed from all modules and a cross reference added to the same figure in the core protocol instead. Change made to limit the number of modules requiring updating during a protocol amendment whenever a new module is added.

Section 6.2.1 Durvalumab preparation and handling: Clarification that if the final product is stored at both refrigerated and ambient temperatures, the total time should not exceed 24 hours.

Section 6.4 Treatment compliance: Clarification that patients must return all containers and any remaining tablets at their next scheduled treatment cycle, not just at the end of the study. Clarification that dose reductions for durvalumab are not permitted.

Section 6.6 Dose modification and discontinuation: Text updated to state that any patient requiring a toxicity related dose delay of more than 28 days from the last day of dosing must be discontinued from the study unless there is approval from the Study Physician for the patient to continue. Change made to align with Module 8.

Section 8.4.5.2 Management of AZD6738-related toxicities: Statement added that if a side effect requires drug interruption longer than 28 days, re-starting study medication should be discussed with the study physician.

Version 6.0, 05 November 2019

Key amendments and rationale for changes:

Table 1 Schedule of Activities: Footnote added that ad-hoc collection of survival status may be requested for OS analyses

Section 2.2.1.2 Durvalumab data: Text updated to align with Edition 15 of the durvalumab IB.

Figure 2 Study flow diagram: Updated to reflect the addition of Modules 6 and 7.

Section 4.3.1 Justification of durvalumab dose: Correction of typographical errors and to align with Edition 15 of the durvalumab IB.

Section 6.2.1 Durvalumab preparation and handling: Change to the window around the duration of durvalumab infusion to ±15 minutes. The previous window of ±5 minutes was considered too restrictive.

Section 6.2.2 Study drug administration: Clarified that AZD6738 twice daily doses should be administered approximately 12 hours apart.

Section 6.4 Treatment compliance: Instructions on how to record treatment compliance with AZD6738 updated for clarity.

Table 4 Prohibited medications: Information on the rationale for the prohibition of EGFR TKIs added.

Version 5.0, 19 March 2019

Key amendments and rationale for changes:

Table 1 Schedule of Activities – Treatment intervention period (Module 3):

- Clarified that tumour evaluation scans are required until objective disease progression, up to and including the 90-day safety follow-up period.
- Updated in line with the core protocol, to replace modified RECIST 1.1 with RECIST 1.1, to ensure comparability with other NSCLC study results. Updated for consistency across all modules of the study.

Figure 1 Study design: Updated to clarify that patients with locally advanced disease are included, and to specify CCI at pre-screening.

Section 2 Introduction and **Section 4.1 Overall design:** Amended in line with inclusion criterion 5 in the core clinical study protocol (CSP), which clarified the required prior treatment in response to questions from investigators. According to the study's main objective, patients must have had disease progression on a prior anti-PD-1/PD-L1 therapy. The patient must have also received a prior platinum doublet though it is not

required to have had disease progression whilst receiving treatment with the platinum doublet therapy.

Section 2.1 Study rationale: Clarification that there is currently no established therapy for patients who have developed resistance to PD-1/PD-L1 and platinum-doublet therapies.

Section 2.2 Background: Indication text updated to reflect status of approvals for durvalumab (IB Edition 14, 11 February 2019).

Section 2.2.1.1 Overview of durvalumab: Indication text updated to reflect status of approvals for durvalumab (IB Edition 14, 11 February 2019).

Section 2.2.1.2 Durvalumab data: PACIFIC overall survival data and Study CD-ON-MEDI4736-1108 efficacy data updated in line with the IB for durvalumab (IB Edition 14, 11 February 2019).

Section 2.2.2.2 AZD6738 data: Study information and data updated in line with the IB for AZD6738 (IB Edition 7, 16 November 2018).

Section 2.2.3 Durvalumab and AZD6738 in combination: Data updated for Study D5330C00004 per data cut-off 13 June 2018.

The following sections have been updated in line with the core durvalumab Clinical Study Protocol (CSP), in which the Toxicity Management Guidelines (TMGs) for durvalumab have been removed from the main body of the CSP template and moved to a standalone annex. TMG versioning will be independent of the protocol allowing for consistency across the durvalumab clinical development programme. Updated for consistency across all modules of the study.

- Section 6.2.1 Durvalumab preparation and handling
- Section 6.6 Dose modification and discontinuation
- Section 8.4.5.1 Management of durvalumab-related toxicities

Figure 2 Study flow diagram: Footnote added to specify that per protocol version 3.0, Module 4 (durvalumab + vistusertib) is closed to recruitment.

Section 5.3.1 Restrictions applicable to durvalumab: Noted that topical corticosteroids are permitted.

Section 6.2.1 Durvalumab preparation and handling: Updated for clarity and alignment with product insert.

Section 6.2.3 Study drug administration and **Table 8 Dose interruption and stopping criteria:** The dosing window for AZD6738 was clarified. **Section 6.2.3 Study drug administration:** Updated in line with the core protocol, to replace modified RECIST 1.1 with RECIST 1.1, to ensure comparability with other NSCLC study results. **Section 6.4 Treatment compliance** and **Section 6.6 Dose modification and discontinuation:** Clarified that dose reductions are not allowed for durvalumab without prior agreement with the study physician. **Section 6.6 Dose modification and discontinuation:** Section header amended for consistency with other modules; text changed from 'temporary discontinuation' to 'treatment interruption' for clarity. **Table 7 Schedule of Activities for patients re-allocated to second on-treatment period (Module 3):** Updated to clarify that informed consent and screening period to confirm eligibility for re-allocation will be performed within 28 days before dosing and to cross refer to the eligibility criteria in Table 1 of the core CSP.
Version 4.0, 26 October 2018
Updated version number to keep in line with changes made in the core CSP. No other changes were made in this appendix.
Version 3.1, 31 July 2018
Key amendments and rationale for changes: **Table 1 Schedule of Activities:** Update to the durvalumab ADA sampling schedule in CCI Sampling is still required pre-dose on Cycle 1 Day 1 and Cycle 2 Day 1, but is now also subsequently required Q12W within the first year and Q24W in the second year of treatment. Addition of a ±7 day window around the study discontinuation and follow-up visits. Removal of WHO/ECOG assessments: these will now only be performed at screening to reduce the burden on sites. **Section 2.2 Background:** Updates to durvalumab and AZD6738 background information in light of emerging data. **Figure 2 Flow diagram:** Updated to reflect the addition of Module 5 to the protocol.

Section 5.2 Exclusion criteria (Module 3-specific): Addition of exclusion K-12 Inability to swallow the formulated product.

Section 5.3.1 Restrictions applicable to durvalumab: Amended to extend the period patients should not receive live vaccines to 180 days after the last dose of study drug. Updated for consistency across all modules of the study.

Table 4 Prohibited medications: Updated to align with updated exclusion criteria in the core protocol.

Section 6.2.3 Study drug administration: Text moved from the module to the core protocol and amended to allow patients to continue receiving treatment with monotherapy if, in the opinion of the treating physician, they are deriving benefit.

Table 7 Schedule of Activities for patients re-allocated to second on treatment period: Addition of a ±7 day window around the study discontinuation and follow-up visits. Removal of WHO/ECOG assessments: these will now only be performed at screening to reduce the burden on sites

Version 2.0, 26 February 2018

Key amendments and rationale for changes:

IND number updated following advice from the FDA to conduct HUDSON under its own IND, which cross references IND 119833.

Table 1 Schedule of activities and Table 7 Schedule of activities for patients re-allocated to second on treatment period were updated to include:

- The new dosing schedule for AZD6738, recommended from new information to be 240 mg BD for 1 week, with a cycle 0 lead-in, then on days 22-28 of subsequent cycles
- On treatment mandatory biopsy was moved to cycle 2, day 1
- The requirement for pregnancy tests, for women of child bearing potential, on day 1 of every cycle, whilst the patient is on treatment.

Figure 1 Study design: For patients who are re-allocated to a second treatment within HUDSON, the "screening assessments as per schedule of assessments in the treatment specific module" was corrected to state "as per schedule of assessments **in the core protocol**".

2.2.1 Durvalumab: Background information added in line with the new durvalumab IB Edition 12.

2.2.2.2 AZD638 data and 2.2.3 Durvalumab and AZD6738 in combination: up-to-date information on new clinical studies was included.

Figure 2 Study Flow Diagram: Based on observations from other studies exploring the hypothesis of CCI [redacted] have been removed as biomarkers of interest in HUDSON.

4.3.1 Justification for durvalumab dose and 4.3.2 Justification for AZD6738 dose:

- Information added on dose justification of durvalumab in line with the new IB Edition 12.
- Based on new information, the AZD6738 dose recommended for HUDSON was confirmed as 240 mg BD for 1 week.

5.1 Inclusion criteria (Module 3-specific): the numbering of the inclusion criteria was corrected from K-3 to K-2.

5.2 Exclusion criteria: Exclusion criterion K-5, "Globular Filtration Rate estimated by MDRD and CKD-EPI is standardised to a body surface area of 1.73 m2" is not deemed appropriate when subject may be frail. Therefore, renal impairment will be assessed using creatinine clearance, as calculated by the Cockcroft-Gault equation.

5.3 Lifestyle restrictions:

- Blood donation guidance updated to be in line with the new durvalumab IB Edition 12. Section also revised to 'refer to section 5.3 of the core protocol'.
- Information about reproduction restrictions is included within the core protocol to ensure consistency in reproduction and contraception requirements across each module. Patients will be required to adopt birth control methods (and avoid the donation of sperm) from screening until 6 months after the last dose of study drug.

The following sections have also been updated in line with the AZD6738 recommended dose:

- Table 2 Study drugs
- 6.2.2 Study drug administration of AZD6738,
- Table 3 Treatment schedule
- Table 6 AZD6738 dose modifications for toxicity management
- Table 7 Schedule of activities for patients re-allocated to second on treatment period.

6.2.3 Study drug administration: Patients allocated to a biomarker matched cohort who, in the opinion of the treating physician would benefit from continued treatment with AZD6738 whilst durvalumab is discontinued, may continue treatment with prior approval from the study physician. This text was also added to section **6.6 Dose modification** for clarity.

6.5.2 Effect of AZD6738 on other drugs: Additional guidelines were included on avoiding concomitant medications, herbal supplements and/or ingestion of foods that significantly modulate CYP3A4 or P-gp activity.

6.6 Dose modification: Clarification of dose modification rules, including:

- If patients' body weight falls ≤30 kg during the study, (s)he will be withdrawn from the study treatment unless (s)he derives some clinical benefit according to the treating physician. This text was also added to section **6.2.1 Durvalumab preparation and handling** for clarity.
- Management of dose interruptions of durvalumab and AZD6738.

Table 7 Schedule of activities for re-allocation of treatment: Footnote added to clarify that eligibility criteria for both core CSP and this module are applicable.

8.2.3 Vital signs; Table 1 SoA and Table 7 SoA for re-allocation of treatment: addition of requirement for blood pressure and pulse rate to be measured in the supine, sitting and standing positions.

8.4.5.2 Management of AZD6738-related toxicities: Acceptable levels of ANC and platelets were relaxed.

10. References: Updated in line with the additional information provided in section 2.2.1.

Various administrative changes.

Version 1, 05 September 2017
Initial Creation

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

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1. PROTOCOL SUMMARY

1.1 Schedule of Activities (SoA)

The Schedule of Activities (SoA) for the lead-in and on-treatment period for Module 3 is shown in Table 1 below, and for the optional re-allocated second on-treatment period in Section 7, Table 7. For the SoA for the pre-screening and main screening visits, please refer to the core protocol.

Table 1 Schedule of Activities – Treatment intervention period (Module 3)

	Cycle 0 (7-day lead-in)	**C1** 28 days Weeks 1-4		**C2** 28 days Weeks 5-8		**C3 - etc** **All cycles 28 days**	**Study drug disc.** (28 days after study drug disc.)	**Safety follow-up** (90 days after study drug disc.)	**Survival follow up**	**Notes**
Week	**1**	**1**	**4**	**5**	**8**	**9, 13, 17 etc**				
Day of cycle	**1**	**1**	**22**	**1**	**22**	1				
Window (days)	**0**[a]	**±2**	**±2**	**±2**	**±2**	**±2**	**±7**	**±7**	**±7**	
Study procedures[c]										
Physical examination	X	X	X	X	X	X	X			Section 8.2.2 (core protocol)
Vital signs[b]	X	X	X[f]	X	X[f]	X	X			Section 8.2.3 (core protocol)
ECG	X	X		X		X				Section 8.2.4 (core protocol)
Concomitant medications	X	X	X	X	X	X	X			Section 6.5
Laboratory assessments[c]										
Clinical chemistry	X	X	X[f]	X	X[f]	X	X			Section 8.2.1 (core protocol). If screening laboratory assessments are performed within 3 days prior to Day 1 they do not need to be repeated
Haematology[e]	X	X	X[f]	X	X[f]	X	X			
APTT and INR	X	As clinically indicated								

	Cycle 0 (7-day lead-in)	**C1** 28 days Weeks 1-4		**C2** 28 days Weeks 5-8		**C3 - etc** **All cycles 28 days**	**Study drug disc.** (28 days after study drug disc.)	**Safety follow-up** (90 days after study drug disc.)	**Survival follow up**	**Notes**
Week	**1**	**1**	**4**	**5**	**8**	**9, 13, 17 etc**				
Day of cycle	**1**	**1**	**22**	**1**	**22**	1				
Window (days)	**0**[a]	**±2**	**±2**	**±2**	**±2**	**±2**	**±7**	**±7**	**±7**	
TSH, free T_3 and free T_4	X	X	X	X	X	X	X			Section 8.2.1 (core protocol)
Urinalysis	X	As clinically indicated								Section 8.2.1 (core protocol)
Pregnancy test	X	X		X		X	X			Section 8.2.1.2 (core protocol)
AE/SAE	X	X	X	X	X	X	X	X		Section 8.3 (core protocol)
Study drug administration[c,d]										
Durvalumab		X		X		X				Section 6.1
AZD6738	X Days 1-7		X Days 22-28		X Days 22-28	X Days 22-28				Section 6.1
Drug accountability	X	X	X	X	X	X	X			Section 6.2.4
Other administration										
Blood for [redacted] assessments[i]	X	X		X		X[i]	X			Section 8.8 (core protocol)
Circulating soluble factors	X	X	X	X	X	X (Cycle 4 only)	X			Section 8.8 (core protocol)
Whole blood for gene expression (PAXgene RNA tubes)	X	X	X	X	X	X (Cycle 4 only)	X			Section 8.8 (core protocol)

	Cycle 0 (7-day lead-in)	**C1** 28 days Weeks 1-4		**C2** 28 days Weeks 5-8		**C3 - etc** **All cycles 28 days**	**Study drug disc.** (28 days after study drug disc.)	**Safety follow-up** (90 days after study drug disc.)	**Survival follow up**	**Notes**
Week	**1**	**1**	**4**	**5**	**8**	**9, 13, 17 etc**				
Day of cycle	**1**	**1**	**22**	**1**	**22**	1				
Window (days)	**0[a]**	**±2**	**±2**	**±2**	**±2**	**±2**	**±7**	**±7**	**±7**	
Whole blood for flow cytometry[j]	X	X	X	X	X	X (Cycle 4 only)	X			Section 8.8 (core protocol)
TCR immuno-sequencing	X	X	X	X	X	X (Cycle 4 only)	X			Section 8.8 (core protocol)
Blood sample for ADA for durvalumab (pre-dose except at safety follow up)		X		X		X (C5D1) then Q12W in first year, then Q24W in second year		X		Section 8.5.3 (core protocol)
Tumour evaluation (CT or MRI, RECIST 1.1)			Every 6 weeks ±1 week for the first 24 weeks relative to the start of combination therapy (Cycle 1 Day 1), then every 8 weeks ±1 week thereafter, until objective disease progression as defined by RECIST 1.1 and confirmed with a subsequent scan (in the absence of clinically significant deterioration)							Section 8.1 (core protocol)
Biopsy on treatment (mandatory)[k]				X						Section 8.8 (core protocol). This should align with the first RECIST assessment
Biopsy on disease progression (mandatory only for re-allocated patients[g])							X			Section 8.8 (core protocol)

	Cycle 0 (7-day lead-in)	**C1** 28 days Weeks 1-4		**C2** 28 days Weeks 5-8		**C3 - etc** **All cycles 28 days**	**Study drug disc.** (28 days after study drug disc.)	**Safety follow-up** (90 days after study drug disc.)	**Survival follow up**	**Notes**
Week	**1**	**1**	**4**	**5**	**8**	**9, 13, 17 etc**				
Day of cycle	**1**	**1**	**22**	**1**	**22**	1				
Window (days)	**0**[a]	**±2**	**±2**	**±2**	**±2**	**±2**	**±7**	**±7**	**±7**	
Subsequent cancer therapy								X	X	Section 8.1.3.1 (core protocol). To be done every 3 months
Survival status									X[h]	Section 8.1.3.1 (core protocol). To be done every 3 months

[a] Every effort should be made to minimise the time between allocation and starting treatment. Note, if main screening assessments have been performed within 3 days prior to C0D1, then assessments do not need to be performed on C0D1 pre-dose.

[b] If clinically indicated, blood pressure to be measured in the supine and standing positions after at least 10 minutes' rest.

[c] Following the final data cut-off for the module CSR (see Section 9.4.2 of the core protocol), any patients on study treatment may continue on treatment and should be assessed for safety according to standard local clinical practice. Study drug administration, SAE reporting and related safety assessment data should be recorded in the eCRF until 90 days after study drug discontinuation, when the patient will end participation in the study. The other assessments for the study will no longer be performed and those data will no longer be collected; the tumour evaluations will be performed as per standard of care. The survival follow-up will no longer be conducted.

[d] A + 2-day window is allowed for durvalumab administration; in each treatment cycle, starting with Cycle 1, AZD6738 administration will start 21 days after durvalumab infusion.

[e] Eosinophil, monocyte, lymphocyte and neutrophil counts will be recorded for patients dosed in expanded cohorts as part of the routine white blood cell count for safety assessment and will be collected retrospectively for patients already enrolled in the expanded cohorts.

[f] Haematology, clinical chemistry and vital sign assessments will take place on Day 22 (± 2-day window) of Cycles 1 and 2. If any toxicity is detected during these additional safety assessments, the patient will be managed as per the protocol, and as clinically indicated. In the event that a patient has an event of thrombocytopenia, anaemia and/or neutropenia that is ≥ Grade 3 during the first 2 cycles, this additional safety assessment will be included in subsequent cycles until there is no evidence of ≥ Grade 3 thrombocytopenia, anaemia and/or neutropenia for at least 2 cycles.

[g] From implementation of protocol v10.0, optional treatment re-allocation of patients to a second treatment cohort is no longer applicable.

[h] Ad hoc collection of survival status may be requested for overall survival analyses.

[i] Whole blood to be taken every cycle for the first 3 cycles and then at every radiographic assessment visit (every 6 weeks [± 1 week] for the first 24 weeks relative to the start of combination therapy [C1D1], then every 8 weeks [± 1 week]) in all patients (at pre-dose on durvalumab dosing day) until disease progression (or study treatment discontinuation).

[j] If a flow cytometry sample is not collected at the C0D1 visit, there is no requirement to collect further samples for analysis at subsequent study visits.

[k] On-treatment biopsy is not required if a fresh tumour sample is not collected at pre-screening.

ADA Anti-drug antibodies; AE adverse event; APTT activated partial thromboplastin time; C cycle; CD8+ cytotoxic T-cell; CSR clinical study report; CT computed tomography; CCI D day; ECG electrocardiogram; eCRF electronic Case Report Form; INR international normalised ratio; RECIST 1.1 Response Evaluation Criteria in Solid Tumours 1.1; MRI magnetic resonance imaging; PBMC peripheral blood mononuclear cell; PD-1 programmed cell death-1; Q12W every 12 weeks; Q24W every 24 weeks; SAE serious adverse event; TCR T-cell receptor repertoire; TSH thyroid-stimulating hormone; T_3 triiodothyronine; T_4 thyroxine.

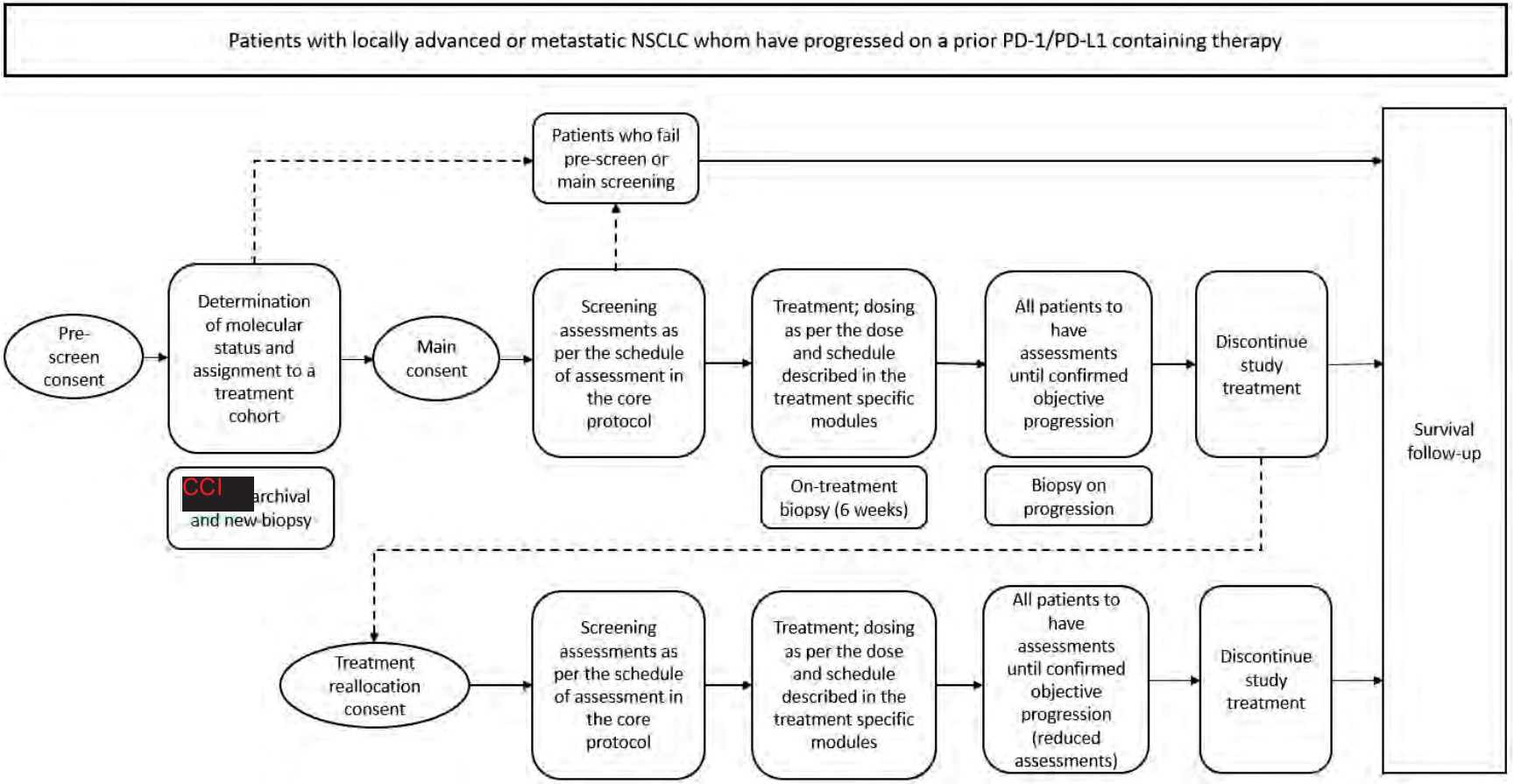
1.2 Synopsis

Please refer to Section 1.2 of the core protocol.

1.3 Schema

The general study design is summarised in Figure 1.

Figure 1 Study design



Note, as of implementation of protocol v10.0, survival follow-up of screen failures and optional treatment re-allocation to a different treatment is no longer applicable.

CCI NSCLC non-small cell lung cancer; PD-1 programmed cell death-1; PD-L1 programmed cell death-ligand 1.

2. INTRODUCTION

Study D6185C00001 (HUDSON) is a Phase II, open-label, multi-centre umbrella study in patients who have received an anti-programmed cell death-1 (PD-1)/anti-programmed cell death-ligand 1 (PD-L1) containing therapy and a platinum-doublet regimen for locally advanced or metastatic non-small cell lung cancer (NSCLC) either separately or in combination. The patient must have had disease progression on a prior line of anti-PD-1/PD-L1 therapy. The modular design allows the evaluation of the efficacy, safety, and tolerability of multiple study drugs. This module to the core study protocol describes Module 3, which will investigate the efficacy, safety, and tolerability of durvalumab administered in combination with AZD6738.

2.1 Study rationale

As described in Section 2.2 of the core protocol, immune checkpoint inhibitors targeting the PD-1/PD-L1 pathway have shown significant activity in the first- and second-line treatment settings in patients with NSCLC. However, it is becoming evident that there is a new and significant patient population emerging that does not respond to anti-PD-1/PD-L1 containing therapy (primary resistance) or progresses during anti-PD-1/PD-L1 containing therapy (acquired resistance). There is currently no established therapy for patients who have developed resistance to PD-1/PD-L1 and platinum-doublet therapies, and novel treatments for these patients are urgently needed.

The aim of this umbrella study (D6185C00001) is to investigate multiple study drugs for the treatment of NSCLC in molecularly matched and non-matched patient populations after failure of immune checkpoint inhibitors, to identify patient populations who may respond favourably to novel anti-tumour therapies.

2.2 Background

Durvalumab and AZD6738 are both currently in clinical development as anti-cancer therapies in a variety of malignancies. Durvalumab as a weight-based regimen of 10 mg/kg every 2 weeks (Q2W) has been approved for use in the treatment of patients with urothelial carcinoma (UC). On 16 February 2018, durvalumab was approved in the US for the treatment of patients with unresectable Stage III NSCLC. On 21 September 2018, durvalumab was approved in the European Union (EU) for the treatment of locally advanced, unresectable NSCLC in adults whose tumours express PD-L1 on ≥1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy. As of 12 July 2019, durvalumab is approved in over 45 countries for NSCLC. On 27 March 2020, the Food and Drug Administration approved durvalumab in combination with etoposide and either carboplatin or cisplatin as first-line treatment of patients with extensive-stage small cell lung cancer.

Module 3 will investigate both agents in combination, to test the hypothesis that the combination will result in complementary anti-tumour activity. Brief background on AZD6738 and durvalumab, including their mechanisms of action, is provided below. For detailed descriptions of the chemistry, pharmacology, efficacy, and safety of AZD6738 and durvalumab, refer to the respective Investigator's Brochures.

The study will recruit both biomarker-matched and biomarker non-matched patients (see Section 4.1). The biomarker is the enzyme ATM (see Section 2.2.1).

2.2.1 Durvalumab

2.2.1.1 Overview of durvalumab

Expression of PD-L1 protein is an adaptive immune response that helps tumours evade detection and elimination by the immune system. PD-L1 can be induced by inflammatory signals (eg, interferon-gamma) and can be expressed on both tumour cells and tumour-associated immune cells in tumour microenvironment. PD-L1 blocks T-cell function and activation through interaction with PD-1 and CD80 (B7.1). By binding to its receptors, PD-L1 reduces cytotoxic T-cell activity, proliferation, and cytokine production. Durvalumab is a fully human, high affinity, immunoglobulin G1 kappa monoclonal antibody that selectively blocks the interaction of PD-L1 with PD-1 and cluster of differentiation (CD)80 (B7.1) while leaving PD-1/ programmed cell death ligand-2 interaction intact. Durvalumab does not induce antibody dependent cell-mediated cytotoxicity. Selective blockade of PD-L1/PD-1 and PD-L1/CD80 interactions enhances antitumour immune responses. These antitumour responses may result in tumour elimination.

Durvalumab is approved in a number of territories including the US, EU, Japan, Canada and Brazil under the brand name IMFINZI™ Injection.

The recommended dose as per the IMFINZI package insert is 10 mg/kg administered as an IV infusion over 60 minutes every 2 weeks (Q2W).

For more information, please refer to the latest version of the Durvalumab Investigator's Brochure.

2.2.1.2 Durvalumab data

To date, durvalumab has been given to more than 12000 patients as part of ongoing studies either as monotherapy or in combination with other anticancer agents. Details on the safety profile of durvalumab monotherapy are summarised below. Refer to the current durvalumab IB for a complete summary of pre-clinical and clinical information including safety, efficacy, and pharmacokinetics (PK).

Clinical activity in locally advanced NSCLC

The efficacy of durvalumab was evaluated in the PACIFIC Study, a randomised, double-blind, placebo-controlled, multicentre study in CCI patients with histologically or cytologically confirmed locally advanced, unresectable NSCLC. Patients had completed definitive platinum-based chemoradiation within 1 to 42 days prior to initiation of the study and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Ninety-three percent of patients had received a total dose of 54 to 66 Gy of radiation. The study excluded patients who had progressed following concurrent chemoradiation therapy, patients with active or prior documented autoimmune disease within 2 years of initiation of the study; a history of immunodeficiency; a history of severe immune-mediated adverse reactions; medical conditions that required systemic immunosuppression, except physiological dose of systemic corticosteroids; active tuberculosis or hepatitis B or C or HIV infection or patients receiving live attenuated vaccine within 30 days before or after the start of durvalumab. Patients were randomised 2:1 to receive 10 mg/kg durvalumab (n=476) or 10 mg/kg placebo (n=237) via IV infusion Q2W for up to 12 months or until unacceptable toxicity or confirmed disease progression. Randomisation was stratified by gender, age (<65 years vs. ≥65 years) and smoking status (smoker vs. nonsmoker). Patients with disease control at 12 months were given the option to be re-treated upon disease progression. Tumour assessments were conducted every 8 weeks for the first 12 months and then every 12 weeks thereafter.

The demographics and baseline disease characteristics were well balanced between study arms. Baseline demographics of the overall study population were as follows: male (70%), age ≥65 years (45%), White (69%), Asian (27%), other (4%), current smoker (16%), past-smoker (75%), and never smoker (9%), World Health Organization (WHO)/ECOG PS 0 (49%), WHO/ECOG PS 1 (50%). Disease characteristics were as follows: Stage IIIA (54%), Stage IIIB (44%), histological subgroups of squamous (47%), non-squamous (53%), PD-L1 expression in tumour cells (TC)≥25% (22%), PD-L1 expression TC<25% (41%). (PD-L1 status was retrospectively analysed using the Ventana PD-L1 [SP263] Assay in 451 patients with available samples, taken prior to concurrent chemoradiation therapy).

At the time of the interim progression-free survival (PFS) analysis, the median PFS by blinded independent central review (BICR) was significantly longer with durvalumab treatment (16.8 months) compared with placebo (5.6 months); hazard ratio 0.52; 98.9% CI: 0.39, 0.70; p<0.0001. At the time of the interim overall survival (OS) analysis, the median OS was not reached for the durvalumab arm and was 29.1 months for the placebo arm; hazard ratio, 0.69; 95% CI, 0.55, 0.86). The 36-month OS rate was 57.0% with durvalumab vs 43.5% with placebo.

Clinical activity in recurrent and metastatic NSCLC

Based on current data from the Study CD ON MEDI4736-1108 (NCT01693562), evidence of clinical activity with durvalumab has been observed. The following responses were observed in patients with NSCLC.

Overall, clinical activity was observed in both the PD-L1 high (defined as having tumour cells [TC] ≥25%) and PD-L1 low/negative (defined as TC <25%) subgroups, however, patients with PD-L1 high tumours had higher objective response rates (ORRs).

The ORR per BICR was 21.8% and 6.4% in patients with PD-L1 high and low/negative tumours, respectively and 15.3% in the overall population regardless of PD-L1 expression. The ORR was 25.9%, 14.3% and, 11.5% in the 1L, 2L and 3L+ cohorts, respectively. Median duration of response (DOR) was 17.74 months. Median OS was 12.4 months; median OS was 21.0, 11.8 and 9.3 months in the 1L, 2L and 3L+ cohorts, respectively. The OS rate at 24 months was 29.6% (Antonia et al 2019).

The ATLANTIC study in third-line or higher NSCLC showed higher ORR and survival outcomes in high PD-L1 positive patients. Across cohorts the ORR ranged from 3 to 43%, median progression-free survival (PFS) ranged from 1.8 to 5.5 months and median OS ranged from 5.9 to 13.6 months but was not reached at the time of initial reporting in the >90% PD-L1 expressors. The ORR and survival outcomes reported in durvalumab studies are in keeping with other similar agents targeting the PD-1/PD-L1 axis (Garassino et al 2017).

Preliminary efficacy data from the MYSTIC study in first-line advanced or metastatic NSCLC showed that in PD-L1 high (≥25% TC) NSCLC, median PFS by BICR was 4.7 months for durvalumab monotherapy and 5.4 months for chemotherapy; hazard ratio of 0.87; 99.5% CI: 0.593, 1.285; p=0.324. The median OS was 16.3 months for the durvalumab arm and 12.9 months for the chemotherapy arm; hazard ratio for death was 0.76; 97.54% CI: 0.564, 1.019; p=0.036. The 24-month OS rate was 38.3% vs 22.7% and the 12-month PFS rate was 32.3% vs 14.3% for the durvalumab and chemotherapy arms respectively. When durvalumab was administered in combination with tremelimumab, the median PFS by BICR was 3.9 months for durvalumab + tremelimumab and 5.4 months for chemotherapy; hazard ratio of 1.05; 99.5% CI: 0.722, 1.534; p=0.705. The median OS was 11.9 months for the durvalumab +tremelimumab arm and 12.9 months for the chemotherapy arm; hazard ratio for death was 0.85; 98.77% CI: 0.611, 1.173; p=0.202. The 24-month OS rate was 35.4% vs 22.7% and the 12-month PFS rate was 25.8% vs 14.3% for the durvalumab + tremelimumab and chemotherapy arms respectively (Rizvi et al 2020).

Immuno-oncology agents targeting the PD-1/PD-L1 pathway have demonstrated activity as monotherapy and in combination with chemotherapy in patients who are immunotherapy-naïve. However, the present study will recruit patients who either have primary resistance to

anti-PD-1/PD-L1 therapy or who developed acquired resistance while on anti-PD-1/PD-L1 therapy. Thus, in this immunotherapy-resistant setting, durvalumab will be administered in combination with an agent that has a different and complementary mechanism of action in order to maximise the likelihood of clinical activity.

2.2.2 AZD6738

2.2.2.1 Overview of AZD6738

AZD6738 is a potent, selective inhibitor of ataxia telangiectasia and Rad3-related protein (ATR), with good selectivity against other phosphatidylinositol 3-kinase-related kinase (PIKK) family members. This compound is being developed as an oral anti-tumour agent as monotherapy or in combination with the checkpoint inhibitor durvalumab (anti-PD-L1), polyadenosine 5'diphosphoribose (poly [ADP ribose]) polymerisation (PARP) inhibitors, or DNA-damaging radiotherapy or chemotherapy, in patients with DNA damage response (DDR)-deficient tumours.

ATR is a serine/threonine protein kinase and member of the PIKK family. During normal DNA replication, ATR is activated by persistent single strand DNA breaks (SSBs) that occur if a replication fork is stalled in S-phase during DNA synthesis. Activation of ATR triggers a signal cascade leading to cell cycle arrest in S-phase whilst the DNA is repaired and the stalled replication fork resolved. Without repair, SSBs can progress to double strand DNA breaks (DSBs), the most genotoxic form of DNA damage due to the consequences DSBs have for accurate chromosome segregation during cell division (O'Connor 2015). ATR is also recruited to single-strand DNA coated with Replication Protein A following single-strand DNA damage or the resection of DSBs.

AZD6738 is an inhibitor of ATR that blocks this activity, causing stalled replication forks to collapse leading to DSBs and a dependence on ATM, a key enzyme coordinating the cellular response to DSBs (Weber and Ryan 2015). If the level of DNA damage exceeds the capacity to repair, nuclear fragmentation and entry into programmed cell death (apoptosis) occur (Antonia et al 2019; Cimprich and Cortez 2008).

ATM is a closely related kinase that is recruited to DSBs and like ATR, has both checkpoint and repair functions. In normal cells, there is a significant interplay between ATR and ATM as stalled replication forks can be converted into DSBs through further DNA damage and the resection of DSBs generates single-stranded DNA (Stewart et al 2015; Toledo et al 2011). During tumourigenesis, ATM can be inactivated or lost providing a selection advantage for the tumour cell through the increased potential for genome alteration, and an increased dependence on ATR function. Similarly, oncogene activation such as through aberrant Myc, RAS, or cyclin D/E activity, or through tumour suppressor loss such as inactivation of ARID1A or RNA splicing factors (transcription replication collisions) may lead to high levels of replication stress, an accumulation of stalled replication forks, and a dependence on ATR

function for cancer cell survival (Forment and O'Connor 2018; Nguyen et al 2018; Williamson et al 2016).

Preclinically, AZD6738 has demonstrated antitumour activity in gastric cancer cells. In SNU-601 cells with dysfunctional ATM, AZD6738 treatment led to an accumulation of DNA damage due to dysfunctional *RAD51* foci formation, S-phase arrest, and caspase 3-dependent apoptosis, whereas SNU-484 cells with functional ATM were not sensitive to AZD6738. In addition, in an in vivo tumour xenograft mouse model, AZD6738 significantly suppressed tumour growth and increased apoptosis. These findings suggest synthetic lethality between ATR inhibition and ATM deficiency in gastric cancer cells (Min et al 2017).

2.2.2.2 AZD6738 data

Currently, for the ATR programme, there are a number of ongoing AstraZeneca sponsored clinical studies with AZD6738 in addition to HUDSON, where combinations of AZD6738 with carboplatin, olaparib or durvalumab are being explored.

In addition, Study D533BC00001 (LATIFY, NCT05450692) will use AZD6738 plus durvalumab versus standard-of-care docetaxel in patients with NSCLC whose disease has progressed on or after prior anti-PD-(L)1 therapy and platinum-based chemotherapy.

A number of AstraZeneca sponsored studies incorporating AZD6738 are ongoing or completed:

- D419QC00002 study (BALTIC, NCT02937818), using AZD6738 and olaparib combination in patients with platinum refractory extensive-stage small-cell lung cancer, has completed with 21 patients dosed.
- D5336C00001 (VIOLETTE study, NCT03330847) using the AZD6738 and olaparib combination in patients with triple negative breast cancer with BRCA mutation (stratum A), HRR mutation (stratum B) and non-HRR mutation (stratum C), has completed and 109 patients were treated with AZD6738.
- Based on the primary analysis in stratum A of the D5336C00001 study, D6018C00004 (DUETTE, NCT04239014), using the combination of AZD6738 and olaparib as second maintenance treatment in patients with platinum-sensitive relapsed epithelial ovarian cancer, who have previously received PARP inhibitor maintenance treatment, was terminated (no patients were randomised to treatment).
- A previous Phase I study (D5330C00001; NCT01955668) to assess multiple ascending doses of AZD6738 in patients with prospectively identified 11q-deleted relapsed/refractory chronic lymphocytic leukaemia (CLL), prolymphocytic leukaemia (PLL) or B-cell lymphomas was stopped after one patient was treated, due to difficulties in recruitment.
- An AstraZeneca sponsored study (D5330C00008, NCT03328273) tested AZD6738 in combination with acalabrutinib in patients with relapsed/refractory CLL; the monotherapy part of the study was discontinued due to CCI suggesting that

patients had CCI [redacted] with AZD6738 monotherapy, and the study was subsequently terminated early because of operational challenges impacting study execution.

- The platform study for the treatment of relapsed or refractory aggressive non-Hodgkin's lymphoma (Study D9820C00001; PRISM) recruited 2 patients in a treatment module including AZD6738 and acalabrutinib.
- Study D533AC00001 (MONETTE) is using AZD6738 as monotherapy and in combination with durvalumab in patients with unresectable or advanced melanoma who have progressed during treatment with a PD-(L)1 inhibitor ± cytotoxic T-lymphocyte associated protein 4 (CTLA-4) inhibitor.

In addition, there are Externally Sponsored Research (ESR) studies ongoing where AZD6738 is being investigated in combination with olaparib in ovarian cancer (CAPRI study [D5334C00001; NCT03462342]; results from Cohort B have been published [Shah et al 2021]) and in BAF250a (ARID1A)-deficient or BAF250a-expressing advanced solid cancers (D5330C00012; NCT03682289). Completed ERS studies include studies where AZD6738 was investigated as a single agent or in combination with radiotherapy (PATRIOT study [D5330C00002; NCT02223923]), in combination with paclitaxel (Pre-VIKTORY study [D5330C00006; NCT02630199] in patients with advanced solid tumours and enriched with metastatic melanoma [Kim et al 2021]), in combination with durvalumab (VIKTORY study [D6183C00003; NCT02299648] in patients with metastatic melanoma and gastric cancer [Lee et al 2021]), or in combination with olaparib in patients with solid tumours harbouring mutations in homology-directed repair genes (OLAPCO [D0810C00090; NCT02576444]; [Mahdi et al 2021]), in patients with relapsed small cell lung cancer (SUKSES-N2 [D5334C00003; NCT03428607]), and in triple-negative breast cancer (PlasmaMATCH Cohort E [D6184C00001; NCT03182634]).

Anaemia, thrombocytopenia, and neutropenia (including febrile neutropenia), CCI [redacted] have been reported when AZD6738 is used as monotherapy and when used in combination with olaparib or durvalumab.

In general, a higher incidence of haematological toxicities was seen when AZD6738 was used at higher doses, longer schedules, or in combination with myelosuppressive agents. Similarly, the incidence of haematological toxicity was comparatively higher when AZD6738 was administered in patients with haematological malignancies.

Adverse events reported in clinical studies were predictable from pre-clinical data and from what is known about the mechanism of action of AZD6738, the combination drugs given, and/or the underlying disease. The observed toxicities in the clinical setting have been manageable with current clinical practice.

See the current Investigator's Brochure for further information.

The non-clinical and emerging safety profile has not identified any risks that would preclude investigation of AZD6738 in the advanced cancer setting. Based on the identified and potential risks associated with treatment, this protocol incorporates mandatory safety monitoring procedures and additional guidance documents to assist with early diagnosis and rapid management of potential drug-related symptoms.

2.2.3 Durvalumab and AZD6738 in combination

The underpinning hypothesis for combining durvalumab and AZD6738 is that the combination will result in induction of immune memory, leading to more durable control of tumour growth than is achievable with either modality alone. Molecularly targeted therapies may serve as "cancer vaccines" inducing the killing of tumour cells and resulting in the release of tumour antigens and neoantigens, which can then be presented by antigen presenting cells (APCs) to tumour-specific T-cells. These T-cells become activated but also upregulate inhibitory checkpoints such as CTLA-4 and PD-1, which can be blocked with antibodies to permit enhanced anti-tumour T-cell responses, including memory T-cell responses, to enable long-term control of disease and possible cure. In addition, the use of targeted agents to directly kill tumour cells, with release of tumour antigens, may focus the activated immune response generated by immunotherapy agents on tumour antigens rather than self-antigens expressed on normal tissues, resulting in fewer AEs.

Based on our current understanding of the immune response, one can identify 3 distinct steps that must be achieved in order to mount effective anti-tumour immunity (Mellman et al 2011):

1 To initiate immunity, dendritic cells must sample antigens derived from the tumour, mature and differentiate, and ultimately process and present tumour antigens
2 Next, in lymphoid organs, tumour antigen-loaded dendritic cells must generate protective T-cell responses
3 Finally, cancer specific T-cells must enter the tumour bed to perform their function. To do so, they have to overcome the challenge of stromal immune suppression

Single agent PD-1/PD-L1 axis inhibitors primarily impact this third step: relieving stromal suppression. ATR inhibition causes an increase in S-phase DNA damage in tumour cells that is expected to lead to the accumulation of unincorporated DNA fragments in the cytosol, activating the stimulator of interferon genes (STING)/tank binding kinase-1 (TBK1)/interferon regulatory factor-3 (IRF3) innate immune response (Parkes et al 2017). If sufficient DNA damage accumulates, tumour cell death is expected to release tumour specific antigens, changing the tumour microenvironment to promoting antigen presentation (Galluzzi et al 2012). Either consequence of ATR inhibition has the potential to prime the immune response, as outlined in Step 1 above.

Clinical experience of the combination of AZD6738 and durvalumab is summarised in the Investigator's Brochure for AZD6738.

The recommended Phase 2 dose was ascertained from Study D5330C00004 Module 3, in which the following doses were studied:

- Cohort 1 AZD6738 80 mg twice daily (bd) Cycle 0 Days 1 to 14, Cycle 1 Days 22 to 28
- Cohort 2 AZD6738 160 mg bd Cycle 0 Days 1 to 14, Cycle 1 Days 22 to 28
- Cohort 3 AZD6738 320 mg once daily (od) Cycle 0 Days 1 to 14, Cycle 1 Days 22 to 28
- Cohort 4 AZD6738 320 mg od Cycle 0 Days 1 to 14, Cycle 1 Days 15 to 28
- Cohort 5 AZD6738 240 mg bd Cycle 0 Days 1 to 7, Cycle 1 Days 22 to 28
- Cohort 6 AZD6738 240 mg bd Cycle 0 Days 1 to 14, Cycle 1 Days 15 to 28.

AZD6738 240 mg bd Cycle 0 Days 1 to 14, Cycle 1 Days 15 to 28 combined with durvalumab 1500 mg on Day 1 q28 was declared as the recommended Phase II dose.

No reproductive toxicology nor teratogenic studies have been conducted with AZD6738 to date, and it is unknown whether the drug is excreted in human milk. Therefore, women of childbearing potential and men should agree to use adequate contraception prior to study entry and for the duration of study participation, and women who are breast feeding are excluded from the study. Both women and men should be fully informed of the lack of reproductive toxicity testing, and women must have a negative pregnancy test prior to enrolment.

This study will investigate whether the combined effects of AZD6738 and durvalumab can overcome the immune-resistance that has been developed clinically in patients treated with prior PD-1/PD-L1 containing therapy. Clinical responses to AZD6738 in combination with durvalumab have been observed in patients with NSCLC and HNSCC in Study D5330C00004 with tumours that have been characterised as PD-L1 expression low/negative. In total, as assessed by RECIST 1.1, there have been three confirmed partial responses (two NSCLC patients and one squamous cell carcinoma of the head and neck [SCCHN]), one unconfirmed response (NSCLC) and one confirmed complete response in a NSCLC patient. In addition, 12 cases of stable disease have been seen (unclean data, data cut-off 13 June 2018). Accordingly, it is expected that if loss of PD-L1 expression is involved in generation of resistance to front-line PD-1/PD-L1 axis inhibitors that the combination with AZD6738, by removing the dependence on PD-L1 expression, will restore sensitivity.

2.3 Benefit/risk assessment

As described in Section 2.3 of the core protocol, patients recruited to this study are not expected to have other treatment options apart from monotherapy chemotherapy, such as docetaxel. The survival outcome and toxicity profile of chemotherapy in this setting mean that other active therapies are highly desirable and present a potential advantage for patients.

The study design aims to identify patient populations who may respond favourably to novel anti-tumour therapies. Based upon the available non-clinical and clinical safety data, the limited survival benefit provided by the currently available treatment options to patients, the limited life expectancy due to malignant disease, and the hypothesis of the complementary effect of the 2 agents, the investigation of the potential therapeutic efficacy of the combination of durvalumab with AZD6738 in patients with advanced or metastatic NSCLC is acceptable, and the overall benefit/risk assessment supports the proposed study design.

3. OBJECTIVES AND ENDPOINTS

Please refer to the core protocol.

4. STUDY DESIGN

4.1 Overall design

This is an open-label, multi-centre, umbrella study in patients who have received an anti-PD-1/PD-L1 containing therapy and a platinum-doublet regimen for locally advanced or metastatic NSCLC either separately or in combination. The patient must have had disease progression on a prior line of anti-PD-1/PD-L1 therapy. For an overview of the study design see Figure 1; further details on the overall design are provided in Section 4 of the core protocol. For details on the study treatments given in Module 3, see Section 6.1.

Module 3 will evaluate the efficacy, safety and tolerability of durvalumab (given intravenously [IV]) in combination with AZD6738 (given orally) in 3 cohorts of patients: biomarker-matched and biomarker non-matched, as follows:

- **Cohort A.3.ATM** will investigate the efficacy, safety, and tolerability of durvalumab (given IV) in combination with AZD6738 (given orally) in patients who are ATM-deficient (as determined using immunohistochemistry [IHC]), or with detectable aberrations in the *ATM* gene (via next generation sequencing [NGS])
- **Cohorts B.3** will investigate the efficacy, safety, and tolerability of durvalumab (given IV) in combination with AZD6738 (given orally) in patients stratified by prior response to immunotherapy; primary resistance (Cohort B.3.PRI), or acquired resistance (Cohort B.3.ACQ). These terms are defined as follows:
  - Primary resistance; patients who had anti-PD-1/PD-L1 containing therapy but had progression of disease (PD) within ≤24 weeks from the start of treatment.
  - Acquired resistance; patients who had progressive disease >24 weeks from the start of anti-PD-1/PD-L1 containing therapy whilst still on that treatment.

A study flow diagram is provided in the core protocol (Figure 4).

4.2 Scientific rationale for study design

The study aims to identify patient populations who may respond favourably to novel anti-tumour therapies, and the modular design allows evaluation of the efficacy, safety, and tolerability of multiple study drugs. The study requires an open-label design owing to the different schedules and routes of administration of the study drugs.

The scientific background for inclusion of biomarker-matched and biomarker non-matched cohorts is as follows:

- Biomarker-matched cohort A.3.ATM (ATM-deficient): In tumour cells with ATM deficiency, the capacity for DSB repair is reduced so that treatment by AZD6738 leads to DSB accumulation and selective tumour cell death through apoptosis (Vendetti et al 2015). The death of ATM-deficient tumour cells is expected to release tumour antigens and change the tumour microenvironment to promote antigen presentation, priming the immune response (Galluzzi et al 2012). Immune checkpoint blockade by durvalumab at the same time is expected to overcome the inhibitory action of PD-L1 on T-cell activation.
- Biomarker non-matched cohorts B.3.PRI (primary resistant) and B.3.ACQ (acquired resistant): The proliferative drive and genomic instability of cancer cells leads to high background levels of DNA damage and repair. Increasing the levels of S-phase DNA damage by ATR inhibition is expected to lead to the accumulation of unincorporated DNA fragments in the cytosol, activating the STING/TBK1/IRF3 innate immune response, and reversing resistance to immunotherapy (Parkes et al 2017). Checkpoint blockade at the same time by durvalumab is expected to overcome the inhibitory action of PD-L1 on T-cell activation.

4.3 Justification for dose

4.3.1 Justification for durvalumab dose

A durvalumab dose of 20 mg/kg Q4W is supported by in vitro data, pre-clinical activity, clinical PK/pharmacodynamics, biomarkers, and activity data from Study CD-ON-MEDI4736-1108 (hereafter referred to as Study 1108) in patients with advanced solid tumours and from a Phase I study performed in Japanese patients with advanced solid tumour (D4190C00002).

Please refer to the current durvalumab IB for further updates on data from ongoing studies.

PK/Pharmacodynamic data

Based on available PK/pharmacodynamic data from ongoing Study 1108 with doses ranging from 0.1 to 10 mg/kg Q4W or 15 mg/kg Q4W, durvalumab exhibited non-linear (dose dependent) PK consistent with target-mediated drug disposition. The PK approached linearity at ≥3 mg/kg Q4W, suggesting near complete target saturation (membrane-bound and sPD-L1), and further shows that the durvalumab dosing frequency can be adapted to a particular

regimen given the linearity seen at doses higher than 3 mg/kg. The expected half-life with doses ≥3 mg/kg Q4W is approximately 21 days. A dose-dependent suppression in peripheral sPD-L1 was observed over the dose range studied, consistent with engagement of durvalumab with PD-L1. A low level of immunogenicity has been observed. No patients have experienced immune-complex disease following exposure to durvalumab. (For further information on immunogenicity, please see the current durvalumab IB).

A population PK model was developed using the data from Study 1108 (doses=0.1 to 10 mg/kg Q2W or 15 mg/kg Q4W; Fairman et al 2014). Multiple simulations indicate that a similar overall exposure is expected following both 10 mg/kg Q4W and 20 mg/kg Q4W regimens, as represented by AUC_{ss} (4 weeks). Median $C_{max,ss}$ is expected to be higher with 20 mg/kg Q4W (~1.5 fold) and median $C_{trough,ss}$ is expected to be higher with 10 mg/kg Q4W (~1.25-fold). Clinical activity with the 20 mg/kg Q4W dosing regimen is anticipated to be consistent with 10 mg/kg Q4W with the proposed similar dose of 20 mg/kg Q4W expected to (a) achieve complete target saturation in majority of patients; (b) account for anticipated variability in PK, pharmacodynamics, and clinical activity in diverse cancer populations; (c) maintain sufficient PK exposure in case of ADA impact; and (d) achieve PK exposure that yielded maximal anti-tumour activity in animal models.

Given the similar area under the serum drug concentration-time curve (AUC) and modest differences in median peak and trough levels at steady state, the observation that both regimens maintain complete sPD-L1 suppression at trough, and the available clinical data, the 20 mg/kg Q4W and 10 mg/kg Q4W regimens are expected to have similar efficacy and safety profiles, supporting further development with a dose of 20 mg/kg Q4W.

Clinical data

Refer to the current durvalumab IB for a complete summary of clinical information including safety, efficacy, and PK at the 20 mg/kg Q4W regimen.

Rationale for fixed dosing

A population PK model was developed for durvalumab using monotherapy data Study 1108 (CCI doses=0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W; solid tumours). Population PK analysis indicated only minor impact of body weight on the PK of durvalumab (coefficient of ≤0.5). The impact of body weight-based (10 mg/kg Q2W) and fixed dosing (750 mg Q2W) of durvalumab was evaluated by comparing predicted steady state PK concentrations (5th, median, and 95th percentiles) using the population PK model. A fixed dose of 750 mg was selected to approximate 10 mg/kg (based on median body weight of ~75 kg). A total of 1000 patients were simulated using body weight distribution of 40 to 120 kg. Simulation results demonstrate that body weight-based and fixed dosing regimens yield similar median steady state PK concentrations with slightly less overall between-patient variability with fixed dosing regimen.

Similar findings have been reported by others (Narwal et al 2013, Ng et al 2006, Wang et al 2009, Zhang et al 2012). Wang and colleagues investigated 12 monoclonal antibodies and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies (Wang et al 2009). In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-patient variability in PK/pharmacodynamic parameters (Zhang et al 2012).

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar PK exposure and variability, AstraZeneca considered it feasible to switch to fixed dosing regimens. Based on average body weight of 75 kg, a fixed dose of 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) is included in the current study.

An exception to 1500 mg fixed dosing is made for patients with low body weight (below 30 kg). Patients with a body weight of 30 kg or less must receive weight-based dosing, equivalent to 20 mg/kg, until weight increases to greater than 30 kg. At this time, fixed dosing data for patients weighing below 30 kg (corresponding to doses greater than 50 mg/kg) are not available and are not yet supported by product development.

Thus, the clinical activity observed coupled with the safety profile, translational science correlates, and non-clinical data supports further development with a dose of 1500 mg Q4W. The durvalumab dose will not be modified during the study.

4.3.2 Justification for AZD6738 dose

The dose of AZD6738 used in this study is obtained from Module 3 in the dose escalation and expansion cohort of Study D5330C00004 where a total of C patients have been treated. In Cohort 5 investigating AZD6738 240 mg bd 7 days in combination with durvalumab 1500 mg, C patients were treated; in Cohort 6 and the expansion cohort investigating AZD6738 240 mg bd 14 days in combination with durvalumab 1500 mg, a total of C patients have been treated (data cut-off 21 February 2022). Both dose regimens were well-tolerated and 240 mg bd 14 days was later declared – after initiation of the HUDSON study (D6185C00001) –as the recommended Phase II dose. It was decided to investigate 240 mg bd days in this study; AZD6738 240 mg bd Cycle 0 Days 1 to 7 and Cycle 1 (and subsequent cycles). Days 22 to 28 is based on clinical safety and tolerability (mainly CCI safety outcomes) and clinical PK/pharmacodynamic data. In addition, the dose level of 240 mg bd is predicted to CCI AZD6738 concentrations CCI the estimated concentration of an inhibitor where ATR catalytic activity is reduced by CCI threshold for C hours in CCI of patients. In addition, CCI AZD6738 dosing CCI T-cell proliferative burst during the CCI period, potentially promoting upregulation of PD-L1 which can be subsequently blocked with durvalumab to enhance anti-tumour T-cell responses.

Considering emerging PK data from ongoing studies, there is CCI [redacted]

Please refer to the AZD6738 Investigational Medicinal Product Dossier for further information about the dose selection and to the AZD6738 IB for further information around the in vitro threshold values.

4.4 End of study definition

Please refer to the core protocol.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study in order to be assigned to a study cohort. Under no circumstances can there be exceptions to this rule. Patients who do not meet the entry requirements are screen failures; refer to Section 5.4 of the core protocol.

5.1 Inclusion criteria (Module 3-specific)

Patients are eligible to be included in the study only if all the following inclusion criteria apply. Please also refer to the Section 5.1 of the core protocol for the inclusion criteria applicable to all modules in the study. Additional inclusion criteria applicable to Module 3 only are described in this section.

K-1 Patients must fulfil all the core eligibility criteria.

K-2 Identification of molecular aberrations:

- Cohort A.3.ATM: patients who are ATM-deficient (as determined using IHC), or with detectable aberrations in the *ATM* gene (via NGS).

5.2 Exclusion criteria (Module 3-specific)

Patients must not enter Module 3 of the study if any of the following exclusion criteria apply. Refer to Section 5.2 of the core protocol for the exclusion criteria applicable to all modules in the study. Additional exclusion criteria applicable to Module 3 only are described below:

Medical conditions

K-1 Diagnosis of ataxia telangiectasia.

K-2 Refractory nausea and vomiting, chronic gastrointestinal diseases or previous significant bowel resection, with clinically significant sequelae that would preclude adequate absorption of AZD6738.

K-3 Inadequate bone marrow reserve or organ function as demonstrated by any of the following laboratory values: absolute neutrophil count <1.5 x 10^9/L; platelet count <100 x 10^9/L; haemoglobin <90 g/L.

K-4 Persisting (>4 weeks) severe pancytopenia due to previous therapy rather than disease (absolute neutrophil count [ANC] <0.5 x 10^9/L or platelets <50 x 10^9/L).

K-5 Creatinine clearance <45 mL/min calculated by Cockcroft-Gault equation (see Table 5 in the core protocol for the calculation).

K-6 Haematuria: +++ on microscopy or dipstick.

K-7 INR ≥1.5 or other evidence of impaired hepatic synthesis function.

K-8 Alkaline phosphatase >2.5 x upper limit of normal (ULN) (and liver disease unrelated to the tumour). Patients with elevated alkaline phosphatase (ALP) due to tumour related bone metastases or liver metastases will be eligible.

K-9 Patients with relative hypotension (<100/60 mmHg) or clinically relevant orthostatic hypotension, including a fall in blood pressure of >20 mmHg.

Prior/concomitant therapy

K-10 Receiving, or having received, concomitant medications, herbal supplements and/or foods that significantly modulate cytochrome P450 3A4 (CYP3A4) or P-glycoprotein (P-gp) activity (washout periods of 2 weeks, but 3 weeks for St. John's Wort). Note these include common azole antifungals, macrolide antibiotics and other medications.

K-11 Prior exposure to an ATR inhibitor.

Other

K-12 Inability to swallow the formulated product.

For procedures for withdrawal of incorrectly enrolled patients see Section 7.3 of the core protocol.

5.3 Lifestyle restrictions

5.3.1 Restrictions applicable to durvalumab

Patients should not donate blood or blood components while participating in this study and through 90 days after receipt of the final dose of durvalumab or until alternate anticancer therapy is started.

Immunosuppressive medications including, but not limited to systemic corticosteroids at doses beyond 10 mg/day of prednisone or equivalent, methotrexate, azathioprine and tumour

necrosis factor alpha blockers are prohibited. Use of immunosuppressive medications for the management of study drug-related AEs and in patients with contrast allergies is acceptable. In addition, use of topical, inhaled and intranasal corticosteroids is permitted (see Table 4).

Live attenuated vaccines within 30 days of durvalumab dosing are prohibited (ie, 30 days prior to the first dose, during treatment with durvalumab and for 180 days post-discontinuation of durvalumab) (see Table 4). Inactivated viruses, such as those in the influenza vaccine or authorised and approved Coronavirus Disease 2019 (COVID-19) vaccines, are permitted (see Table 5).

5.3.2 Restrictions applicable to AZD6738

Please refer to section 5.3 of the core protocol for contraception requirements.

5.4 Screen failures

Please refer to the core protocol.

6. STUDY TREATMENTS

Study treatment is defined as any study drug(s) (including marketed product comparator and placebo) or medical device(s) intended to be administered to a study participant according to the study protocol. Study treatment in Module 3 refers to durvalumab and AZD6738.

6.1 Treatments administered

6.1.1 Study drugs

Table 2 Study drugs

	AZD6738	Durvalumab
Dosage formulation:	Oral tablets in either 20, 80 or 100 mg	Supplied as a vialed liquid solution containing 500 mg (nominal) durvalumab per vial. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine hydrochloride, 275 mM trehalose dihydrate, 0.02% (w/v) polysorbate 80, at pH 6.0. The nominal fill volume is 10.0 mL.
Route of administration:	Oral	IV infusion
Dosing instructions:	240 mg twice daily in Cycle 0 Days 1-7, followed by 7 days on treatment in each cycle between Days 22 and 28.	Patients enrolled in the study will receive 1500 mg via IV infusion Q4W +2 days (fixed dosing for patients >30 kg body weight).

Table 2 Study drugs

	AZD6738	Durvalumab
Packaging and labelling	Study drug will be provided in high-density polyethylene bottles with child-resistant closures. Labels will be prepared in accordance with GMP and local regulatory guidelines. Label text will be translated into local language, as required. AZD6738 will be provided with either single-panel labels or multi-language booklet labels. Specific dosing instructions will not be included on the label; the site must complete the "Patient Dispensing Card" with the details of the dosing instructions at the time of dispensing. The investigator's emergency contact details will not be on the label, but can be found in the informed consent and the 'Patient Dispensing Card'. For emergency purposes the patient must be in possession of the emergency contact details at all times.	Study drug will be provided in vials. Each vial will be labelled in accordance with GMP and per country regulatory requirement. Labels will be prepared in accordance with GMP and local regulatory guidelines. Label text will be translated into local language, as required. Durvalumab will be provided with either single-panel labels or multi-language booklet labels. The investigator's emergency contact details will not be on the label, but can be found in the informed consent and the 'Patient Emergency Card'. For emergency purposes the patient must be in possession of the emergency contact details at all times.
Provider	AstraZeneca	AstraZeneca. Commercially available 0.9% (w/v) saline or 5% (w/v) dextrose IV bags will be supplied by each site.

bd twice daily; GMP Good Manufacturing Practice; IV intravenous(ly); Q4W every 4 weeks; w/v weight/volume

6.2 Preparation/handling/storage/accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study drugs received and any discrepancies are reported and resolved before use of the study drug.

Only patients enrolled in the study may receive study drugs and only authorised site staff may supply or administer study drugs. All study drugs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study drugs accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study drug are provided in the Pharmacy Manual.

6.2.1 Durvalumab preparation and handling

Durvalumab will be supplied by AstraZeneca as a 500 mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine hydrochloride, 275 mM trehalose dihydrate, and 0.02% (weight/volume [w/v]) polysorbate 80; it has a pH of 6.0 and a density of 1.054 g/mL. The nominal fill volume is 10.0 mL.

Study drug vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. The vials should be kept in the original packaging until use to prevent prolonged light exposure.

The dose of durvalumab for administration must be prepared by the investigator's or site's designated study drug manager using aseptic technique. Total time from needle puncture of the durvalumab vial to the start of administration should not exceed 4 hours at room temperature or 24 hours at 2°C to 8°C (36°F to 46°F). If the final product is stored at both refrigerated and ambient temperatures, the total time should not exceed 24 hours.

A dose of 1500 mg (for patients >30 kg body weight) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab concentration ranging from 1 to 15 mg/mL and delivered through an IV-administration set with a 0.2-µm or 0.22-µm filter. Add 30.0 mL (ie, 1500 mg) of durvalumab to an appropriately sized IV bag such that the final concentration is within 1 to 15 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

If a patient's body weight falls ≤30 kg during the study, (s)he will be withdrawn from the study treatment unless (s)he derives some clinical benefit according to the treating physician. In this case, and following agreement between the treating physician and the Sponsor, the patient may continue treatment at a body-weight adapted dose of 20 mg/kg actual body weight.

Weight-based dosing at 20 mg/kg (for patients ≤30 kg) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab concentration ranging from 1 to 15 mg/mL, and delivered through an IV administration set with a 0.2-µm or 0.22-µm filter. An example of a weight-based dose calculation is shown in Section 6.2.1.1.

Standard infusion time is one hour (±15 minutes), however if there are interruptions during infusion, the total allowed infusion time should not exceed 8 hours at room temperature.

If either preparation time or infusion time exceeds the time limits a new dose must be prepared from new vials. Durvalumab does not contain preservatives, and any unused portion must be discarded.

Do not co-administer other drugs through the same infusion line.

The IV line will be flushed with a volume of IV diluent equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered.

Patients will be monitored before, during, and after the first durvalumab infusion with assessment of vital signs at the times specified in the SoA (Table 1) and Section 8.2.3 of the core protocol. If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be at the investigator's discretion (suggested 30 minutes after each durvalumab infusion). For management of patients who experience an infusion reaction, please refer to the toxicity and management guidelines for infusion-related reactions.

Durvalumab (1500 mg) will be administered via IV infusion Q4W + 2 days. Treatment with durvalumab will commence on Day 1 following confirmation of eligibility and will continue on a Q4W schedule until disease progression is confirmed.

6.2.1.1 Durvalumab weight-based calculation

If a patient's body weight falls ≤30 kg during the study, (s)he will be withdrawn from the study treatment unless (s)he derives some clinical benefit according to the treating physician. In this case, and following agreement between the treating physician and the Sponsor, the patient may continue treatment at a body-weight adapted dose of 20 mg/kg of durvalumab Q4W until the weight improves to >30 kg, at which point the patient should start receiving the fixed dosing of durvalumab 1500 mg Q4W:

1 Cohort dose: X mg/kg

2 Patient weight: Y kg

3 Dose for patient: XY mg = X (mg/kg) × Y (kg)

4 Dose to be added into infusion bag:

Dose (mL) = XY mg/50 (mg/mL) where 50 mg/mL is durvalumab nominal concentration. The corresponding volume of durvalumab should be rounded to the nearest tenth mL (0.1 mL). Dose adjustments for each cycle are only needed for greater than 10% change in weight.

5 The number of vials required for dose preparation is the next greatest whole number of vials from the following formula:
Number of vials = Dose (mL) / 10.0 (mL/vial)

Example:

1 Cohort dose: 20 mg/kg
   (a) Patient weight: 30 kg
   (b) Dose for patient: 600 mg = 20 (mg/kg) × 30 (kg)

(c) Dose to be added into infusion bag:
Dose (mL) = 600 mg / 50 (mg/mL) = 12.0 mL

(d) The number of vials required for dose preparation:
Number of vials = 12.0 (mL) / 10.0 (mL/vial) = 2 vials

6.2.2 Study drug administration

Following a 7-day lead-in period (Cycle 0, AZD6738 monotherapy), each treatment cycle will span 28 days, as shown in Table 3.

Administration of AZD6738

When AZD6738 is administered, patients must fast (water to drink only) for at least 2 hours prior to taking a dose, to at least 1 hour post-dose for all doses.

AZD6738 will be administered for 7 days in Cycle 0 Days 1 to 7. AZD6738 will be administered orally 240 mg twice daily, approximately 12 hours apart, starting on Day 22 until Day 28 of each treatment cycle, starting with Cycle 1. Patients are allowed to take the scheduled dose up to 2 hours after the scheduled dose time. If greater than 2 hours, the missed dose should not be taken and patient should continue with next dose at allotted time. If patient wishes to bring forward the time of their scheduled dose, the dose can be taken up to a maximum of 2 hours prior to the scheduled time, ie, ±2-hour window.

Administration of durvalumab

Following preparation of durvalumab (see Section 6.2.1), the entire contents of the IV bag should be administered as an IV infusion over approximately 60 minutes (±15 minutes).

Table 3 Treatment schedule, AZD6738 in combination with durvalumab

	Cycle 0	Cycle 1 (and beyond)		
	7-day lead-in	D1	D2 to D21	D22 to D28
AZD6738 (oral, bd)	X[a]			X
Durvalumab (IV)		X		

[a] AZD6738 monotherapy administered on each day of the 7-day lead-in.
D day; IV intravenous; bd twice daily.

Patients should continue to receive study treatment (ie, durvalumab in combination with AZD6738) until objective radiological disease progression as per Response Evaluation Criteria in Solid Tumours (RECIST 1.1), as long as, in the investigator's opinion, they are benefiting from treatment and they do not meet any other discontinuation criteria. Disease progression should be confirmed by a subsequent scan (no earlier than 4 weeks later) in the absence of clinically significant deterioration as assessed by the investigator. All patients who have objective progression of disease will enter follow-up.

6.2.3 Storage

All study drugs should be kept in a secure place under appropriate storage conditions.

The AZD6738 product label on the bottle specifies the appropriate storage.

Durvalumab is to be stored at the study centre in a secured facility with limited access and controlled temperature (2ºC to 8ºC). The study drug storage temperature should be monitored on a daily basis and documented in the temperature monitoring log according to the study drug handling instructions.

The study drug must be kept in the original outer container and under conditions specified on the labels.

In the following cases, the centre staff should not use affected study drug and should immediately contact AstraZeneca representative for further guidance:

- Temperature excursion upon receipt or during storage at the study
- Damaged kit upon receipt
- Damaged vial/bottle

Damaged study drug should be documented according to the instructions provided by AstraZeneca representative. Storage conditions stated in the Investigator's Brochure, or the study drug Handling Instructions document, may be superseded by the label storage.

6.2.4 Accountability

The study drugs provided for this study should only be used as directed in the study protocol.

The study site staff will account for all study drugs received at the centre, for unused study drugs, and for appropriate destruction (according to local procedures). Certificates of delivery, destruction, and/or return should be signed.

The administration of all medications (including study drug) and details of treatment with study drug should be recorded in the appropriate sections of the electronic Case Report Form (eCRF).

6.3 Measures to minimise bias: randomisation and blinding

This is an open-label study.

Recruitment to the biomarker-matched cohorts will be based upon a predefined schema (described in the Pathology and Genomic Testing Manual) for patient allocation which takes account of biomarker prevalence estimates and the platform of evidence for each study treatment.

Recruitment into the biomarker non-matched arms will be conducted in a sequential manner.

If a patient withdraws from participation in the study, then his/her enrolment code cannot be reused. Withdrawn patients will not be replaced.

6.4 Treatment compliance

The administration of all study drugs should be recorded in the appropriate sections of the eCRF. Durvalumab will be administered on site. Treatment compliance will be assured by reconciliation of site drug accountability logs. Patients will record their oral AZD6738 dosing on a diary which should be returned to the site at the next available visit. Sites should additionally record AZD6738 doses taken at site visits.

Patients will self-administer AZD6738. Patients should be given clear instructions on how and when to take their study treatment. Study site staff will make tablet counts at regular intervals during treatment. Compliance will be assessed by the tablet count and the information will be recorded in the appropriate section of the eCRF. After the tablet count has been performed, the remaining tablets will not be returned to the patient but will be retained by the investigative site until reconciliation is completed by the study monitor. All patients must return their bottle(s) of AZD6738 at the appropriate scheduled visit, when a new bottle will be dispensed. Patients will be instructed to notify study site personnel of missed doses. Dates of missed or held doses will be recorded by the patient on their patient diary and by the site staff on the eCRF.

Patients must return all containers and any remaining tablets at their next scheduled treatment cycle and at the end of the study.

Any change from the dosing schedule, dose interruptions, dose reductions, dose discontinuations should be recorded in the eCRF. Note: Dose reductions are not allowed for durvalumab (see Section 6.6).

The Study Drug Storage Manager is responsible for managing the study drug from receipt by the study site until the destruction or return of all unused study drug. The investigator(s) is/are responsible for ensuring that the patient has returned all unused study drug.

Use of study treatment in doses in excess of that specified in the protocol is considered to be an overdose. Refer to Section 8.4.3 for procedures in case of overdose.

6.5 Concomitant therapy

Any medication or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the patient is receiving at the time of enrolment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Prohibited concomitant medications are described in Table 4. Please refer to Section 8.4.5 for guidance on management of study drug-related toxicities.

The use of concomitant medications must be recorded in the eCRF.

Table 4 Prohibited medications

Prohibited medication/class of drug:	
Unless stated otherwise, these medications are prohibited from the time that patients enter the main screening period until the last dose of study treatment. The pre-screen may be done whilst on prior therapy.	
Any investigational anticancer therapy other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment
Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment. (Note: concurrent use of hormones for non-cancer-related conditions [eg, insulin for diabetes and hormone replacement therapy] is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable [eg, by local surgery or radiotherapy]). Patients may receive treatment with bisphosphonates or RANKL inhibitors for the treatment of bone metastases
Immunosuppressive medications, including, but not limited to: systemic corticosteroids at doses exceeding 10 mg/day of prednisone or its equivalent, methotrexate, azathioprine, and tumour necrosis factor-α blockers	Should not be given concomitantly, or used for premedication prior to the infusions. The following are allowed exceptions: • Use of immunosuppressive medications for the management of study drug-related AEs • Short-term premedication for patients receiving combinations where the prescribing information for the agent requires the use of steroids for documented hypersensitivity reactions • Use in patients with contrast allergies • In addition, use of inhaled, topical, and intranasal corticosteroids is permitted. A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of non-immunotherapy related events experienced by the patient (eg, chronic obstructive pulmonary disease, radiation, nausea, etc).
Live attenuated vaccines	Prohibited from the time that patients enter the main screening period until 180 days after the last dose of study treatment.
Epidermal growth factor receptor (EGFR) Tyrosine kinase inhibitors (TKIs)	Should not be given concomitantly. Should be used with caution in the 90 days post last dose of durvalumab. Increased incidences of pneumonitis (with third generation EGFR TKIs) and increased incidence of transaminase increases (with 1st generation EGFR TKIs) have been reported when durvalumab has been given concomitantly.
Herbal and natural remedies which may have immune-modulating effects	Should not be given concomitantly unless agreed by the sponsor

AE adverse event

The use of herbal preparations/medications should be discouraged throughout the study. These herbal medications include, but are not limited to: St. John's Wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone, yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 7 days prior to first dose of study drug (3 weeks for St John's Wort). Use of these products, as well as use of all vitamins, nutritional supplements and all prescribed concomitant medications, must be recorded in the eCRF.

Other concomitant treatment

Medication other than that described above, which is considered necessary for the patient's safety and wellbeing, may be given at the discretion of the investigator and recorded in the appropriate sections of the eCRF.

6.5.1 Rescue and supportive medication

The study site will supply rescue medication, and this will be procured locally. The sponsor will supply only if required by local regulations.

The use of rescue medications is allowable at any time during the study. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

Supportive medication, described in Table 5, may be given at the discretion of the investigator and recorded in the appropriate sections of the eCRF.

Table 5 Supportive medication

Supportive medication/class of drug:	Usage:
Concomitant medications or treatments (eg, acetaminophen or diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care, except for those medications identified as "prohibited," as listed above	To be administered as prescribed by the investigator
Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy to non-target lesions, etc])	Should be used, when necessary, for all patients AZD6738 treatment should be discontinued for a minimum of 3 days before a patient undergoes palliative radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.
Inactivated viruses, such as those in the influenza vaccine or authorised and approved COVID-19 vaccines.	Permitted. Administration of COVID-19 vaccines should be avoided for 72 hours prior to administration of the first dose of study treatment.

COVID-19 Coronavirus Disease 2019.

6.5.2 Effect of AZD6738 on other drugs

Avoid concomitant medications, herbal supplements and/or ingestion of foods that significantly modulate CYP[CCI] or [CCI] activity (see guidelines below). Note: These include common azole antifungals, macrolide antibiotics, etc (please refer to Section 11 for details on AZD6738 drug-drug interactions). In the absence of discontinuation criteria, if the Investigator feels that concomitant administration of medications, herbal supplements or foods that significantly modulate CYP[CCI] activity is necessary based upon medical judgement, such products may be administered with caution following discussion between the investigator and the study physician.

Concomitant medication may be given as medically indicated with the following exceptions:

- The principal enzyme for metabolising AZD6738 is CYP[CCI]. Patients should avoid concomitant drugs, herbal supplements, and/or ingestion of foods known to modulate CYP[CCI] activity from the time they enter the screening period until 28 days after the last dose of study medication.
- AZD6738 is an inducer of CYP[CCI] CYP[CCI] and CYP[CCI] and showed weak inhibition of CYP[CCI] CYP[CCI] and CYP[CCI] Caution should be applied with co-administration of drugs that are either completely metabolised by CYP[CCI] and/or CYP[CCI] or CYP[CCI] or CYP[CCI] or that are substrates of CYP[CCI] and/or CYP[CCI] CYP[CCI] and CYP[CCI] and also have a narrow therapeutic index. Investigators should be aware that the exposure of other drugs metabolised by CYP[CCI] CYP[CCI] and/or CYP[CCI] may be increased and exposure of other drugs metabolised by CYP[CCI] and/or CYP[CCI] may be reduced.
- Strong CYP[CCI] inducers. For patients taking any of these drugs the required washout periods prior to starting AZD6738 is 2 weeks, except for St. John's Wort, which is 3 weeks.
- Prior to study medication, use of potent inducers or inhibitors of CYP[CC] are not permitted. For subjects taking any of these drugs, the required wash-out periods before starting AZD6738 is five half-lives; except for St. John's wort, which is 3 weeks.
- On study medication, if there is no suitable alternative concomitant medication other than a potent inhibitor of CYP[CCI] the investigator must interrupt AZD6738 for the duration of the potent CYP[CC] inhibitor and wait for the required wash-out period (five half-lives) before dosing AZD6738 again. If potent CYP[CC] inducers are considered necessary for the patient's safety and welfare, this may diminish the clinical efficacy of AZD6738 and the patient should be monitored carefully for any change in the efficacy of study treatment.
- AZD6738 is also a [CCI] substrate. Co-administration of [CCI] inhibitors or inducers may affect exposure to AZD6738 and therefore should not be co-administered with AZD6738 (please refer to Section 11 for details on AZD6738 drug-drug interactions). If the use of any inhibitors or inducers of [CCI] are considered necessary for the patient's safety and welfare, the investigator must interrupt AZD6738 for the duration of the [CCI] inhibitor or

inducer and wait for the required wash-out period of the CCI modulator (five half-lives) before dosing with AZD6738.

- AZD6738 is a substrate of CCI. Co-administration of CCI inhibitors or inducers may affect exposure to AZD6738 (please refer to Section 11 for details on AZD6738 drug-drug interactions); therefore, it is recommended that the investigators must interrupt AZD6738 for the duration of the CCI inhibitor or inducer and wait for the required wash-out period of the CCI modulator (five half-lives) before dosing AZD6738 again.
- AZD6738 is an inhibitor of CCI Co-administration of substrates of CCI may affect exposure to AZD6738; therefore, it is recommended that caution should be applied when such drugs are to be administered with AZD6738.
- The use of any natural/herbal products or other 'folk remedies' (and medications and foods that significantly modulate CYPCC) should be discouraged. If deemed necessary, such products may be administered with caution and the reason for use documented in the eCRF.
- Anticoagulation therapy: patients on warfarin may participate in this study but it is recommended that their INR is monitored more frequently.

6.6 Dose modification and discontinuation

For patients who weigh ≥30 kg, the dose of durvalumab cannot be modified. If a patient's body weight falls below 30 kg during the study, (s)he will be withdrawn from the study treatment unless (s)he derives some clinical benefit according to the treating physician. In this case, and following agreement between the treating physician and the Sponsor, the patient may continue treatment at a body-weight adapted dose of 20 mg/kg actual body weight.

Durvalumab dosing can be interrupted in the event of treatment-related toxicity. All toxicities will be graded according to Common Toxicity Criteria for Adverse Events (CTCAE) version 4.03. Dose reductions are not permitted. In case of doubt, the investigator should consult with the study physician. Please refer to the toxicity management guidelines for durvalumab.

Dose adjustments for AZD6738 will be based on the organ system exhibiting the greatest degree of toxicity. Dose reductions or interruptions, and initiation of supportive care, are allowed as deemed appropriate by the treating physician. If Day 1 treatment with durvalumab is delayed, then AZD6738 will not resume until 22 days after the durvalumab dose is given. If durvalumab is delayed due to AZD6738-induced toxicity, please contact the sponsor for agreement on continuation of study therapy. Where a toxicity related event arises before AZD6738 is started within a cycle, AZD6738 must be started within up to 50 days from the prior administration of durvalumab. If the onset of AZD6738 is delayed, the onset of the subsequent durvalumab administration will need to be delayed accordingly. Where AZD6738 has been started within a given cycle, is interrupted and resumed within the planned 7-day dosing period, the patient must complete only the AZD6738 doses remaining until the last day

of the planned 7-day period. There will be no opportunity to recover for any missed AZD6738 doses. If AZD6738 cannot be resumed within the planned 7-day period, then the patient will proceed to the next cycle, as planned. Any patient requiring a toxicity related dose delay of more than 50 days from the last day of dosing must be discontinued from the study treatment unless there is approval from the Study Physician for the patient to continue. A patient may continue on monotherapy if the other treatment is permanently stopped for drug-specific toxicity (not where the toxic effect is common to both drugs) (core protocol Section 7.1.1).

Study treatment should be stopped at least 3 days prior to planned surgery. After surgery study treatment can be restarted when the wound has healed. No stoppage of study treatment is required for any biopsy procedure.

Table 6 AZD6738 dose modifications for toxicity management (7-day schedule)

Dose level	AZD6738
Initial dose	240 mg bd Days 22-28
1st dose reduction	160 mg bd Days 22-28
2nd dose reduction	160 mg od Days 22-28
3rd dose reduction	Stop treatment

Management of study drug-related toxicities is described in detail in Section 8.4.5.

6.7 Treatment after the end of the study

Patients are permitted to either receive standard of care therapy, or to continue to receive study treatment following the end of the study if, in the opinion of the investigator, they are continuing to receive benefit from treatment. After discontinuation of study treatment, the investigator will be at liberty to define further most appropriate anti-cancer treatment. Subsequent anti-cancer treatment is expected to be initiated following the cancer recurrence or development of a new cancer. Information on subsequent anti-cancer therapies should be recorded on the clinical database.

7. DISCONTINUATION OF TREATMENT AND PATIENT WITHDRAWAL

Please refer to Section 7 in the core protocol. Guidance on optional re-allocation to a second treatment cohort is provided in Section 7.4 of the core protocol. Stopping criteria for AZD6738 are in Section 8.4.5.2 of this module.

Study procedures and their timing for patients re-allocated to a second study treatment are summarised in the re-allocation SoA (Table 7).

Note: As of implementation of protocol v10.0, optional treatment re-allocation of patients to a different treatment cohort is no longer applicable.

Table 7 Schedule of activities for patients re-allocated to second on-treatment period (Module 3)

	Cycle 0 (7 day lead-in)	**C1** (28 days) Weeks 1-4		**C2** (28 days) Weeks 5-8		**C3 – etc** All cycles 28 days	**Study drug disc.** (28 days after study drug disc.)	**Safety follow-up** (90 days after study drug disc.)	**Survival follow up**	**Notes**
Week	**1**	**1**	**4**	**5**	**8**	**9, 13, 17 etc**				
Day of cycle	**1**	**1**	**22**	**1**	**22**	**1**				
Window (days)	**0**[a]	**±2**	**±2**	**±2**	**±2**	**±2**	±7	±7	±7	
Study procedures										
Informed consent	X									Section 5.2.1 (core protocol). Patient must consent to new treatment. Will be performed within 28 days before dosing
Eligibility criteria for re-allocation[b]	X									Patients must meet eligibility criteria in the core CSP (see Table 1) and in this module
Physical examination	X	X	X	X	X	X	X			Section 8.2.2 (core protocol)
Vital signs[c]	X	X	X	X	X	X	X			Section 8.2.3 (core protocol)
ECG	X	X		X		X				Section 8.2.4 (core protocol)
Concomitant medications	X	X	X	X	X	X	X			Section 6.5
Laboratory assessments										
Clinical chemistry	X	X	X	X	X	X	X			Section 8.2.1 (core protocol). If screening laboratory assessments are performed within 3 days prior to Day 1 they do not need to be repeated
Haematology	X	X	X	X	X	X	X			
APTT and INR		As clinically indicated								
TSH, free T_3 and free T_4	X	X	X	X	X	X	X			Section 8.2.1 (core protocol)
Urinalysis		As clinically indicated								Section 8.2.1 (core protocol)
Pregnancy test	X	X		X		X	X			Section 8.2.1.2 (core protocol)
AE/SAE assessment	X	X	X	X	X	X	X	X		Section 8.3 (core protocol)

Table 7 Schedule of activities for patients re-allocated to second on-treatment period (Module 3)

	Cycle 0 (7 day lead-in)	**C1** (28 days) Weeks 1-4		**C2** (28 days) Weeks 5-8		**C3 – etc** All cycles 28 days	**Study drug disc.** (28 days after study drug disc.)	**Safety follow-up** (90 days after study drug disc.)	**Survival follow up**	**Notes**
Week	**1**	**1**	**4**	**5**	**8**	**9, 13, 17 etc**				
Day of cycle	**1**	**1**	**22**	**1**	**22**	**1**				
Window (days)	**0**[a]	**±2**	**±2**	**±2**	**±2**	**±2**	±7	±7	±7	
Study drug administration										
Durvalumab		X		X		X				Section 6.1
AZD6738	X (Days 1-7)		X (Days 22-28)		X (Days 22-28)	X (Days 22-28)				Section 6.1
Drug accountability	X	X	X	X	X	X	X			Section 6.2.4
Other administration										
Subsequent cancer therapy								X	X	These assessments are repeated here from Table 1. Patients will be followed for survival from the original treatment cohort. These are not additional assessments for re-allocation, they are only repeated here for completeness.
Survival status									X	

[a] Every effort should be made to minimise the time between allocation to treatment and starting treatment.
[b] Eligibility criteria in core CSP and in this module apply.
[c] If clinically indicated, blood pressure to be measured in the supine and standing positions after at least 10 minutes' rest.

Note, if main screening assessments have been performed within 3 days prior to C0D1, then assessments do not need to be performed on C0D1 pre-dose.

AE adverse event; APTT activated partial thromboplastin time; C cycle; ECG electrocardiogram; INR international normalised ratio; SAE serious adverse event; TSH thyroid-stimulating hormone; T_3 triiodothyronine; T_4 thyroxine.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in the SoA (Table 1). Study procedures and their timing for patients re-allocated to a second study treatment are summarised in the re-allocation SoA (Table 7).

8.1 Efficacy assessments

Please refer to the core protocol.

8.2 Safety assessments

8.2.1 Clinical safety laboratory assessments

As part of the white blood cell count safety assessment, eosinophil and monocyte counts will be recorded for patients dosed in the expanded cohorts and recorded retrospectively for patients already enrolled in the expanded cohorts.

Please refer to core protocol.

8.2.1.1 Coagulation

Please refer to core protocol.

8.2.1.2 Other safety assessments

Please refer to core protocol.

8.2.1.3 Pneumonitis (interstitial lung disease) investigation

The following assessments, and additional assessments if required, will be performed to enhance the investigation and diagnosis of potential cases of pneumonitis. The results of the assessment will be collected.

- Physical examination; Signs and symptoms (cough, shortness of breath and pyrexia, etc) including auscultation for lung field will be assessed.
- Saturation of peripheral oxygen (SpO_2)
- Other items; When pneumonitis (interstitial lung disease [ILD]) is suspected during study treatment, the following markers should be measured where possible:
  - ILD markers (KL-6, SP-D) and β-D-glucan
  - Tumour markers: Particular tumour markers which are related to disease progression.

8.2.2 Physical examinations

Please refer to core protocol.

8.2.3 Vital signs

Please refer to section 8.2.3 in the core protocol. However, if clinically indicated, eg, in the event of clinically relevant symptoms such as pre-syncope or dizziness, blood pressure will be measured in the supine and standing positions after at least 10 minutes' rest. Assessments will be performed at the visits as shown in the SoA (Table 1) and for the optional re-allocated second on-treatment period in Section 7, Table 7.

8.2.4 Electrocardiograms

Please refer to core protocol.

8.2.5 Performance status

Please refer to core protocol.

8.3 Collection of adverse events

Please refer to the core protocol.

8.4 Safety reporting and medical management

8.4.1 Reporting of serious adverse events

Please refer to the core protocol.

Any myeloid malignancies (ie., MDS and/or AML) should be reported whenever this has been observed in the follow-up of the patients.

8.4.2 Pregnancy

Please refer to the core protocol.

8.4.3 Overdose

Please refer to the core protocol.

8.4.4 Medication error

Please refer to the core protocol.

8.4.5 Management of study drug-related toxicities

8.4.5.1 Management of durvalumab-related toxicities

Please refer to the toxicity management guidelines for durvalumab.

8.4.5.2 Management of AZD6738-related toxicities

If a patient experiences a clinically significant and/or unacceptable toxicity, dosing will be interrupted and supportive therapy administered as required.

If the toxicity resolves or reverts to CTCAE Grade ≤1 or 2 (depending on the toxicity), treatment with AZD6738 may be restarted using the rules in Table 8 for dose modifications. Patients who are at the lowest possible dose, or who had their dose previously reduced to the lowest possible dose and who have demonstrated an acceptable response to the dose interruption may be permitted to restart at the lowest dose level at the discretion of the Investigator.

If the toxicity does not resolve to CTCAE Grade ≤1 or 2 or the patient is not showing clinical benefit, then the patient should be discontinued from treatment and observed until resolution of the toxicity.

Any patient requiring a toxicity related dose delay of more than 28 days from the planned onset of AZD6738 (ie, 50 days from the last administration of durvalumab), must be discontinued from the study treatment, unless there is approval from the study physician for the patient to continue.

If a patient develops severe haematologic toxicity or blood transfusion dependence, treatment with AZD6738 should be interrupted and appropriate haematologic testing should be initiated. If the blood parameters remain clinically abnormal after 4 weeks of AZD6738 dose interruption, bone marrow analysis and/or blood cytogenetic analysis are recommended. If myeloid malignancies are confirmed whilst on treatment with AZD6738, it is recommended that AZD6738 should be discontinued and the patient be treated appropriately. AEs of myeloid malignancies should be monitored by conventional AE collection and reporting, additionally any cases should be reported after the 30-day follow-up period irrespective of Investigator causality.

The dose of AZD6738 must not be adjusted under any other circumstances than those described in this section unless prior agreement is given by the Sponsor.

All dose modifications and interruptions (including any missed doses) and the reasons for the modifications/interruptions are to be recorded in the eCRF.

Table 8 Dose interruption and stopping criteria (7-day schedule)

Event	Action
Grade 1-2 toxicities (except Grade 2 neutropenia and thrombocytopenia)	AZD6738 dosing may continue with supportive treatment (as required) or investigator decision whether to interrupt AZD6738 (max 28 days). Following interruption, AZD6738 may be resumed at the same dose level.

Table 8 Dose interruption and stopping criteria (7-day schedule)

Event	Action
Grade 2 neutropenia or Grade 3 anaemia	Blood counts may recover during the "off drug period" on the intermittent schedule. AZD6738 dosing may continue with supportive treatment (as required e.g. transfusion) or investigator decision whether to interrupt AZD6738 (max 28 days). Following interruption, AZD6738 may be resumed at the same dose level or dose reduced by 1 level[a].
Grade 2-3 thrombocytopenia	**First occurrence** Interrupt AZD6738 (max 28 days) until platelets improve to ≥75,000/mm^3. Following interruption, AZD6738 may be resumed at the same dose level, as blood counts may recover during the "off period" on the intermittent schedule. If blood counts do not recover by the start of the next dosing period, AZD6738 should be restarted with a dose reduction by 1 level[a]. **Subsequent occurrences** Interrupt AZD6738 (max 28 days) until platelets improve to ≥75,000/mm^3. Following interruption, ceralasertib should be restarted with a dose reduction by 1 level[a].
Grade 4 thrombocytopenia	Interrupt AZD6738 (max 28 days) and give appropriate supportive treatment until platelets improve to ≥75,000/mm^3. Following interruption, AZD6738 should be restarted with a dose reduction by 1 level[a].
Grade 3-4 toxicity (including Grade 3-4 neutropenia or Grade 4 anaemia) *Excludes* Grade 3 anaemia or Grade 3-4 thrombocytopenia (see above)	**First occurrence** Interrupt AZD6738 (max 28 days) and give appropriate supportive treatment. When toxicity has resolved to grade 1, AZD6738 should be restarted with a dose reduction by 1 level[a]. **Subsequent occurrences** Investigator discretion on whether to interrupt AZD6738 (max 28 days) or to stop treatment. Following interruption, AZD6738 should be restarted with a dose reduction of 1 or 2 levels.
Vomiting	If vomiting occurs shortly after AZD6738 is swallowed, the dose should only be replaced if all of the intact tablets can be counted. Resume with the following scheduled dose.
Missed dose	Allowed to take the scheduled dose up to 2 hours after the scheduled dose time. If greater than 2 hours, the missed dose should not be taken and the patient should continue with next dose at the allotted time.

[a] This table is for guidance. Therefore, for example, it may be deemed appropriate by the Investigator to reduce the dose by more than 1 dose level depending on the individual patient circumstances.

Individual stopping criteria:

Hepatic

- ALT or AST or ALP* > 5 × ULN

- ALT or AST or ALP* > 3 × ULN with the appearance of symptoms associated with a clinical diagnosis of hepatitis including right upper quadrant pain or tenderness, fever, rash or eosinophilia (> 5%)
- [ALT or AST > 3 × ULN] and [total bilirubin > 2 × ULN or INR+ > 1.5 or other evidence of impairment to the synthesis function of the liver]

* In the presence of bone metastasis, assess bone specific isoform of raised ALP in the presence of a raised gamma-GT (to ensure the ALP change is specific to the liver).

+ Unless patient is receiving warfarin.

Please refer to Appendix E "Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law".

Cardiovascular

Clinically significant hypotension defined as an asymptomatic decrease of more than 20 mmHg in systolic blood pressure to below 70 mmHg persisting for at least 10 minutes.

Symptomatic orthostatic fall in systolic blood pressure of more than 20 mmHg compared to resting supine systolic blood pressure.

Haematologic

Patients with suspected or with indications of MDS and/or AML must have the dose of AZD6738 stopped under all circumstances, and evidence of AML/MDS should be ruled out. Further treatment can only be accepted after discussion and agreement with the sponsor.

8.5 Pharmacokinetics

Refer to the core protocol.

8.6 Pharmacodynamics

Pharmacodynamic parameters will be evaluated in this study (see Section 8.6 of the core protocol).

8.7 Genetics

Refer to the core protocol.

8.8 Biomarkers

Refer to the core protocol.

8.9 Medical Resource Utilisation and Health Economics

Medical Resource Utilisation and Health Economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

Refer to the core protocol.

10. REFERENCES

Antonia et al 2019
Antonia SJ, Balmanoukian A, Brahmer J, Ou S-HI, Hellmann MD, Kim S-W, et al. Clinical activity, tolerability, and long-term follow-up of durvalumab in patients with advanced NSCLC. J Thorac Oncol. 2019;14(10)1794-806.

Cimprich and Cortez 2008
Cimprich KA, Cortez D. ATR: an essential regulator of genome integrity. Nat Rev Mol Cell Biol. 2008;9:616-27.

Forment and O'Connor 2018
Forment JV, O'Connor MJ. Targeting the replication stress response in cancer. Pharmacol Ther. 2018;188:155-67

Galluzzi et al 2012
Galluzzi L, Senovilla L, Zitvogel L, Kroemer G. The secret ally: immunostimulation by anticancer drugs. Nat Rev Drug Discov. 2012;11(3):215-33

Garassino et al 2017
Garassino M, Vansteenkiste J, Joo-Hang Kim, Hervé Léna, Mazières J, Powderly J, Dennis P, Huang Y, Wadsworth C, Rizvi N. PL04a.03: Durvalumab in ≥3rd-Line Locally Advanced or Metastatic, EGFR/ALK Wild-Type NSCLC: Results from the Phase 2 ATLANTIC Study. J Thor Onc. 2017;12:S10-S11.

Kim et al 2021
Kim ST, Smith SA, Mortimer P, Loembé A-B, Cho H, Kim K-M, et al. Phase I study of ceralasertib (AZD6738), a novel DNA damage repair agent, in combination with weekly paclitaxel in refractory cancer. Clin Cancer Res. 2021;27(17):4700-9.

Lee et al 2021
Lee J, Kim ST, Kim K, Lee H, Kozarewa I, Mortimer PGS, et al. Tumor genomic profiling guides patients with metastatic gastric cancer to targeted treatment: The VIKTORY umbrella trial. Cancer Discov. 2019;9(10):1388-405.

Mahdi et al 2021
Mahdi H, Hafez N, Doroshow D, Sohal D, Keedy V, Do KT, et al. Ceralasertib-mediated ATR inhibition combined with olaparib in advanced cancers harboring DNA damage response and repair alterations (olaparib combinations). JCO Precis Oncol. 2021;5:PO.20.00439.

Mellman et al 2011
Mellman I, Coukos G, Dranoff G. Cancer immunotherapy comes of age. Nature. 2011;480:480-9.

Min et al 2017
Min A, Im S-A, Jang H, Kim S, Lee M, Kim DK, et al. AZD6738, a novel oral inhibitor of ATR, induces synthetic lethality with ATM deficiency in gastric cancer cells. Mol Cancer Ther. 2017;16(4);566–77.

Narwal et al 2013
Narwal R, Roskos LK, Robbie GJ. Population Pharmacokinetics of Sifalimumab, an Investigational Anti-Interferonalpha Monoclonal Antibody, in Systemic Lupus Erythematosus. Clin Pharmacokinet. 2013;52:1017–27.

Ng et al 2006
Ng CM, Lum BL, Gimenez V, Kelsey S, Allison D. Rationale for fixed dosing of pertuzumab in cancer patients based on population pharmacokinetic analysis. Pharm Res. 2006;23(6):1275–84.

Nguyen et al 2018
Nguyen HD, Leong WY, Li W, Reddy PNG, Sullivan JD, Walter MJ, et al. Spliceosome mutations induce R loop-associated sensitivity to ATR inhibition in myelodysplastic syndromes. Cancer Res. 2018;78(18):5363-74.

O'Connor 2015
O'Connor MJ. Targeting the DNA Damage Response in Cancer. Mol Cell. 2015;60:547-60.

Parkes et al 2017
Parkes EE, Walker SM, Taggart LE, McCabe N, Knight LA, Wilkinson R et al. Activation of STING-Dependent Innate Immune Signaling By S-Phase-Specific DNA Damage in Breast Cancer. J Natl Cancer Inst. 2017;109(1).

Rizvi et al 2020
Rizvi NA, Cho BC, Reinmuth N, Lee KH, Luft A, Ahn M-J, et al. Durvalumab with or without tremelimumab vs standard chemotherapy in first-line treatment of metastatic non-small cell lung cancer: The MYSTIC Phase 3 randomized clinical trial. JAMA Oncol. 2020;6(5):661-674.

Shah et al 2021
Shah PD, Wethington SL, Pagan C, Latif N, Tanyi J, Martin LP, et al. Combination ATR and PARP Inhibitor (CAPRI): A phase 2 study of ceralasertib plus olaparib in patients with recurrent, platinum-resistant epithelial ovarian cancer. Gynecol Oncol. 2021;163(2):246-253.

Stewart et al 2015
Stewart R, Morrow M, Hammond SA, Mulgrew K, Marcus D, Poon E et al. Identification and characterization of MEDI4736, an antagonistic anti-PD-L1 monoclonal antibody. Cancer Immunol Res. 2015;3(9):1052-62.

Toledo et al 2011
Toledo LI, Murga M, Zur R, Soria R, Rodriguez A, Martinez S et al. A cell-based screen identifies ATR inhibitors with synthetic lethal properties for cancer-associated mutations. Nat Struct Mol Biol. 2011;18:721-7.

Vendetti et al 2015
Vendetti FP, Lau A, Schamus S, Conrads TP, O'Connor MJ, Bakkenist CJ. The orally active and bioavailable ATR kinase inhibitor AZD6738 potentiates the anti-tumor effects of cisplatin to resolve ATM-deficient non-small cell lung cancer in vivo. Oncotarget. 2015;6(42):44289-44305.

Wang et al 2009
Wang DD, Zhang S, Zhao H, Men AY, Parivar K. Fixed dosing versus body size based dosing of monoclonal antibodies in adult clinical trials. J Clin Pharmacol. 2009;49(9):1012-24.

Weber and Ryan 2015
Weber AM, Ryan AJ. ATM and ATR as therapeutic targets in cancer. Pharmacol Ther. 2015;149:124-38.

Williamson et al 2016
Williamson CT, Miller R, Pemberton HN, Jones SE, Campbell J, Konde A, et al. ATR inhibitors as a synthetic lethal therapy for tumours deficient in ARID1A. Nat Commun. 2016;7:13837.

Zhang et al 2012
Zhang S, Shi R, Li C, Parivar K, Wang DD. Fixed dosing versus body size-based dosing of therapeutic peptides and proteins in adults. J Clin Pharmacol. 2012;52(1):18–28.

11. AZD6738 DRUG-DRUG INTERACTIONS

Restrictions regarding drugs affecting CYP[CC] metabolism

There are currently no data confirming that there is a PK interaction between drugs that affect CYP[CC] metabolism and AZD6738; a potential interaction is considered on the basis of preclinical and in vitro data only. AZD6738 is predominantly eliminated via CYP[CC] metabolism, therefore CYP[CC] inhibitors or inducers may increase or decrease exposure to AZD6738, respectively. Potent inhibitors or inducers of CYP[CC] should not be combined with AZD6738. In vitro data also suggest that AZD6738 may be metabolised by CYP[CCI] to a lesser extent, therefore caution should be applied with co-administration of potent inhibitors or inducers of CYP[CCI]

Drugs known to be inhibitors and inducers of CYP[CC] or CYP[CCI] are listed in Table 9 and Table 10, respectively. These lists are not intended to be exhaustive, and similar restrictions will apply to other agents that are known to modulate CYP[CC] or CYP[CCI] activity. Please contact AstraZeneca with any queries on this issue. Please refer to full prescribing information for all drugs prior to co-administration with AZD6738.

Table 9 Drugs known to be inhibitors and inducers of CYP[redacted]

Potent CYP3A inhibitors	Potent CYP[redacted] inducers
boceprevir	apalutamide
ceritinib	avasimibe
clarithromycin	carbamazepine
cobicistat (GS-9350)	ceralasertib
conivaptan	enzalutamide
danoprevir / RIT	ivosidenib
elvitegravir / RIT	lumacaftor
grapefruit juice[a]	mitotane
idelalisib	phenobarbital
indinavir	phenytoin
indinavir /RIT	rifampin
itraconazole	rifapentine
ketoconazole	St John's Wort extract
LCL161	
lopinavir / RIT	
mibefradil	
mifepristone	
nefazodone	
nelfinavir	
posaconazole	
ribociclib	
ritonavir	
saquinavir	
saquinavir / RIT	
telaprevir	
telithromycin	
tipranavir/RIT	
troleandomycin	
VIEKIRA PAK2[b]	
voriconazole	

[a] Double-strength grapefruit juice. Patients should abstain from eating large amounts of grapefruit and Seville oranges (and other products containing these fruits eg, grapefruit juice or marmalade) during the study (eg, no more than a small glass of grapefruit juice (120 mL) or half a grapefruit or 1 to 2 teaspoons (15 g) of Seville orange marmalade daily.

[b] VIEKIRA PAK = 150/100 mg paritaprevir/ritonavir + 25 mg ombitasvir + 800 mg dasabuvir for 28 days.

List created using the University of Washington Drug-Drug Interaction Database July 2019.

RIT Ritonivir. Ritonavir has dual effects of simultaneous CYP[redacted] inhibition and induction, and the net pharmacokinetic outcome during chronic ritonavir therapy is inhibition of CYP[redacted] activity.

Table 10 Drugs known to be inhibitors and inducers of CYP[redacted]

Potent CYP2C8 inhibitors	Potent CYP[redacted] inducers
gemfibrozil clopidogrel	None identified

List created using the University of Washington Drug-Drug Interaction Database Jan 2020.

Drugs known to be inhibitors or inducers of [redacted] undertake appropriate monitoring if co-administration is necessary

AZD6738 is a substrate of [redacted] Co-administration of [redacted] inhibitors/inducers or BCRP inhibitors/inducers may affect exposure to AZD6738, therefore it is recommended that these are not co-administered with AZD6738.

Drugs known to be inhibitors or inducers of [redacted] are listed in Table 11 and Table 12, respectively. These lists are not intended to be exhaustive, and similar restrictions will apply to other agents that are known to modulate [redacted] Please contact AstraZeneca with any queries on this issue. Please refer to full prescribing information for all drugs prior to co-administration with AZD6738.

Table 11 Drugs known to be inhibitors or inducers of CCI

Drugs Known to be Inhibitors of CCI	Drugs Known to be Inducers of CCI
alogliptin	apalutamide
amiodarone	avasimibe
asian ginseng (Panax ginseng)	carbamazepine
asunaprevir	danshen (Salvia miltiorrhiza)
AZD5672	efavirenz
azithromycin	genistein
canagliflozin	green tea
captopril	phenytoin
carvedilol	quercetin
clarithromycin	rifabutin
clopidogrel	rifampin
cobicstat	ritonavir
conivaptan	St. John's wort extract
cremophor EL	tivantinib
cremophor RH	
curcumin	
daclatasvir	
daclatasvir/asunaprevir/beclabuvir	
diltiazem	
diosmin	
dronedarone	
elagolix	
eliglustat	
erythromycin	
felodipine	
five-flavor berry (schisandra chinensis)	
flibanserin	
fluvoxamine	
fostamatinib	
ginkgo	
glecaprevir/pibrentasvir	
indinavir	
indinavir/ritonavir	
isavuconazole	
itraconazole	
ivacaftor	
ketoconazole	
lapatinib	
lopinavir/ritonavir	
mibefradil	

Table 11 Drugs known to be inhibitors or inducers of CCI

mifepristone	
milk thistle	
mirabegron	
nelfinavir	
neratinib	
nifedipine	
nitrendipine	
osimertinib	
paritaprevir/ritonavir/ombitasvir	
paroxetine	
piperine	
propafenone	
quercetin	
quinidine	
quinine	
ranolazine	
rifampin	
ritonavir	
rolapitant	
rucaparib	
saquinavir/ritonavir	
sarecycline	
simeprevir	
sofosbuvir/velpatasvir/voxilaprevir	
St. John's wort extract	
surfactant TPGS	
suvorexant	
talinolol	
telithromycin	
telaprevir	
telmisartan	
tezacaftor/ivacaftor	
ticagrelor	
tipranavir/ritonavir	
tolvaptan	
valbenazine	
valspodar (PSC 833)	
vandetanib	
velpatasvir	
vemurafenib	
verapamil	

Table 11 Drugs known to be inhibitors or inducers of CCI

voclosporin vorapaxar	

List created using the University of Washington Drug-Drug Interaction Database October 2019.

Table 12 Drugs known to be inhibitors or inducers of CCI

Drugs Known to be Inhibitors of CCI	Drugs Known to be inducers of CCI
afatinib aripiprazole curcumin cyclosporine elacridar erlotinib fluvastatin fumitremorgin gefitinib ivermectin lapatinib nilotinib novobiocin pantoprazole pitavastatin ponatinib quercetin quizartinib rabeprazole regorafenib rilpivirine sulfasalazine sunitinib tacrolimus teriflunomide trametinib trifluoperazine vismodegib eltrombopag atazanavir lopinavir ritonavir tipranavir omeprazole	Please check individual drugs on a case-by-case basis

Table 12 Drugs known to be inhibitors or inducers of CCI

estrone 17b-estradiol imatinib mesylate	

List created using http://dmd.aspetjournals.org/content/dmd/43/4/490.full.pdf
Note: Although CCI is involved in a number of clinically relevant DDIs, none of the listed inhibitors above is truly specific for this transporter

Drugs known to be substrates of CYP[CCI] and/or CYP[CCI] or CYP[CCI] or CYP[CCI] undertake appropriate monitoring if co-administration is necessary

AZD6738 is an inducer of CYP[CCI] CYP[CCI] and CYP[CCI] and showed weak inhibition of CYP[CCI] CYP[CCI] and CYP[CCI] Therefore, caution should be applied with co-administration of drugs that are either completely metabolised by CYP[CCI] and/or CYP[CCI] or CYP[CCI] or CYP[CCI] or that are substrates of CYP[CCI] and/or CYP[CCI] CYP[CCI] and CYP[CCI] and also have a narrow therapeutic index (Table 13). Investigators should be aware that the exposure of other drugs metabolised by CYP[CCI] CYP[CCI] and/or CYP[CCI] may be increased, and exposure of other drugs metabolised by CYP[CCI] and/or CYP[CCI] may be reduced.

Table 13 Drugs known to be metabolised by CYP[CCI] and/or CYP[CCI] CYP[CCI] and CYP[CCI]

Metabolised by CYP[CCI]	Metabolised by CYP[CCI]	Metabolised by CYP[CCI]	Metabolised by CYP[CCI]
Abemaciclib (NTR)	agomelatine	daprodustat	benzbromarone
ABT-384	alosetron[a]	dasabuvir	celecoxib
Acalabrutinib (NTR)	caffeine	repaglinide[b]	ibuprofen
alfentanil	duloxetine		(R)-ibuprofen
alisporivir	melatonin		(S)-ibuprofen
almorexant	pirfenidone		glimepiride
alpha-dihydroergocryptine	ramelteon[a]		glipizide
aplaviroc	selegiline[a]		lornoxicam
aprepitant	tacrine		meloxicam
asunaprevir	tasimelteon[a]		piroxicam
atazanavir	tizanidine (NTR)		(S)-warfarin (NTR)
atorvastatin			tolbutamide
avanafil			
avapritinib			
AZD1305			
BIRL 355			
blonanserin			
bosutinib (NTR)			
brecanavir			
brotizolam			
budesonide			
buspirone			
BZF961			
capravirine			
casopitant			
cobimetinib (NTR)			
conivaptan (NTR)			
danoprevir			

Table 13 Drugs known to be metabolised by CYP[CCI] and/or CYP[CCI] CYP[CCI] and CYP[CCI]

darifenacin darunavir dasatinib (NTR) dronedarone ebastine eletriptan eliglustat (in subjects CYP[CCI] PMs) elvitegravir entrectinib (NTR) eplerenone everolimus felodipine ibrutinib indinavir isavuconazole itacitinib ivabradine ivacaftor L-771,688 Levomethadyl/Levacetymethadol (LAAM) (NTR) Lomitapide (NTR) lonafarnib lopinavir lovastatin lumefantrine lurasidone maraviroc midazolam midostaurin (NTR) morphothiadin naloxegol neratinib (NTR) nisoldipine paritaprevir4 perospirone pyrotinib quetiapine ridaforolimus			

Table 13 Drugs known to be metabolised by CYP[CCI] and/or CYP[CCI] CYP[CCI] and CYP[CCI]

saquinavir			
sildenafil			
simeprevir			
simvastatin			
sirolimus			
tacrolimus			
terfenadine			
ticagrelor			
tilidine3			
tipranavir			
tolvaptan (NTR)			
triazolam			
ubrogepant			
ulipristal			
vardenafil			
venetoclax (NTR)			
vicriviroc			
vilaprisan			
voclosporin			
zanubrutinib (NTR)			

[a] Complex Interaction -Substrates metabolized by multiple enzymes, including CYP[CCI]
[b] Repaglinide is also a substrate of [CCI] which might also be inhibited by gemfibrozil or its glucuronide.
List created using the University of Washington Drug-Drug Interaction Database August 2021. Note: This is not an exhaustive list.
(NTR) drug listed in the Narrow Therapeutic Index list by CYP isoform in DrugBank.

Drugs known to be substrates of [CCI] undertake appropriate monitoring if co-administration is necessary

AZD6738 is also an inhibitor of [CCI] Caution should be applied with co-administration of substrates of [CCI] as AZD6738 may increase their exposure.

Drugs known to be substrates of [CCI] are listed in Table 14 and Table 15, respectively. These lists are not intended to be exhaustive and appropriate medical judgment is required. Please contact AstraZeneca with any queries on this issue. Please refer to full prescribing information for all drugs prior to co-administration with AZD6738.

Table 14 Drugs known to be substrates of CCI

docetaxel
enalapril
olmesartan
phalloidin
repaglinide
statins[a]
temocaprilat
valsartan

[a] All statins

List created using https://www.solvobiotech.com/transporters CCI latest access Nov 2019

Table 15 Drugs known to be substrates of CCI

anthracyclines
chlorothiazide
daunorubicin
doxorubicin
imatinib
irinotecan
methotrexate
mitoxantrone
nucleoside analogs
pantoprazole
prazosin
SN-38
topotecan
teriflunomide
rosuvastatin

List created using https://www.solvobiotech.com/transporters/ CCI latest access Nov 2019

Clinical Study Protocol

Drug Substance	Umbrella study
Study Code	D6185C00001 (HUDSON)
Version	14.0
Date	09 October 2024

Appendix L

Module 4: Durvalumab plus vistusertib

An Open-Label, Multi-Drug, Biomarker-Directed, Multi-Centre Phase II Umbrella Study in Patients with Non-Small Cell Lung Cancer, who Progressed on an Anti-PD-1/PD-L1 Containing Therapy (HUDSON)

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

Regulatory Agency Identification Numbers:

EudraCT number: 2017-002208-28

EU CT number: 2023-509004-15-00

IND number: 138050

VERSION HISTORY

Version 14.0, 09 October 2024
Key amendments and rationale for changes: The version number of this module has been revised in line with the other modules in the HUDSON study; however, no changes have been made to this module.

Version 13.0, 14 December 2023
Key amendments and rationale for changes: **Front page:** EU CT number has been added in line with the core CSP.

Version 12.0, 01 March 2023
Key amendments and rationale for changes: The version number of this module has been revised in line with the other modules in the HUDSON study; however, no changes have been made to this module.

Version 11.0, 16 August 2022
Key amendments and rationale for changes: The version number of this module has been revised in line with the other modules in the HUDSON study; however, no changes have been made to this module.

Version 10.0, 12 April 2022
Key amendments and rationale for changes: The version number of this module has been revised in line with the other modules in the HUDSON study; however, no changes have been made to this module.

Version 9.0, 14 May 2021
Key amendments and rationale for changes: The version number of this module has been revised in line with the other modules in the HUDSON study; however, no changes have been made to this module.

Version 8.0, 11 September 2020
The version number of this module has been revised in line with the other modules in the HUDSON study; however, no changes have been made to this module.

Version 7.0, 21 May 2020
Key amendments and rationale for changes: ***The version number of this module has been revised in line with the other modules in the HUDSON study; however, as there are no patients receiving treatment with durvalumab or vistusertib at the time of this amendment, no changes have been made to this module. No additional patients will be treated in this module, per the decision to discontinue vistusertib development in oncology as described previously.***

Version 6.0, 05 November 2019
Key amendments and rationale for changes: ***The version number of this module has been revised in line with the other modules in the HUDSON study; however, as there are no patients receiving treatment with durvalumab or vistusertib at the time of this amendment, no changes have been made to this module. No additional patients will be treated in this module, per the decision to discontinue vistusertib development in oncology as described previously.***

Version 5.0, 19 March 2019
Key amendments and rationale for changes:

This module is being revised in line with changes to the other modules in the HUDSON study, to ensure that modules are consistent where appropriate and that the latest safety information is included. However, it is acknowledged that many of the current revisions are not relevant to the single patient who is under treatment at the time of this amendment. No additional patients will be treated in this module, per the decision to discontinue vistusertib development in oncology as described below.

The following sections have been updated in line with the change to the benefit-risk profile of vistusertib, which has resulted in a decision to discontinue vistusertib development in oncology:

- Section 2.3 Background
- Section 2.4 Benefit/risk assessment

Table 1 Schedule of Activities – Treatment intervention period (Module 4):

- Clarified that tumour evaluation scans are required until objective disease progression, up to and including the 90-day safety follow-up period.
- Updated in line with the core protocol, to replace modified RECIST 1.1 with RECIST 1.1, to ensure comparability with other NSCLC study results. Updated for consistency across all modules of the study.

Figure 1 Study design: Updated to clarify that patients with locally advanced disease are included, and to specify ctDNA at pre-screening.

Section 2 Introduction and **Section 4.1 Overall design:** Amended in line with inclusion criterion 5 in the core clinical study protocol (CSP), which clarified the required prior treatment in response to questions from investigators. According to the study's main objective, patients must have had disease progression on a prior anti-PD-1/PD-L1 therapy. The patient must have also received a prior platinum doublet though it is not required to have had disease progression whilst receiving treatment with the platinum doublet therapy.

Section 2.2 Study rationale: Clarification that there is currently no established therapy for patients who have developed resistance to PD-1/PD-L1 and platinum-doublet therapies.

Section 2.3 Background: Indication text updated to reflect status of approvals for durvalumab (IB Edition 14, 11 February 2019).

Section 2.3.1.1 Overview of durvalumab: Indication text updated to reflect status of approvals for durvalumab (IB Edition 14, 11 February 2019).

Section 2.3.1.2 Durvalumab data: PACIFIC overall survival data and Study CD-ON-MEDI4736-1108 efficacy data updated in line with the IB for durvalumab (IB Edition 14, 11 February 2019).

Section 2.3.2.2 Vistusertib data: Updated in line with IB for vistusertib (Edition 9, 04 December 2018).

Section 4.3.2 Justification for vistusertib dose: Updated in line with IB for vistusertib (Edition 9, 04 December 2018).

Section 5.3.1 Restrictions applicable to durvalumab: Noted that topical corticosteroids are permitted.

The following sections have been updated in line with the core durvalumab Clinical Study Protocol (CSP), in which the Toxicity Management Guidelines (TMGs) for durvalumab have been removed from the main body of the CSP template and moved to a standalone annex. TMG versioning will be independent of the protocol allowing for consistency across the durvalumab clinical development programme. Updated for consistency across all modules of the study.

- Section 6.2.1 Durvalumab preparation and handling
- Section 6.6 Dose modification and discontinuation
- Section 8.4.5.1 Management of durvalumab-related toxicities
- Section 8.4.5.2 Management of vistusertib-related toxicities

Section 6.2.1 Durvalumab preparation and handling: Updated for clarity and alignment with product insert.

Section 6.2.3 Study drug administration: Updated in line with the core protocol, to replace modified RECIST 1.1 with RECIST 1.1, to ensure comparability with other NSCLC study results.

Section 6.4 Treatment compliance, Section 6.6 Dose modification and discontinuation and **Section 8.4.5 Management of study-drug related toxicities** Clarified that dose reductions are not allowed for durvalumab without prior agreement with the study physician.

Section 6.6 Dose modification and discontinuation: Text changed from ‘temporary discontinuation’ to ‘treatment interruption’ for clarity.

Version 4.0, 26 October 2018

Updated version number to keep in line with changes made in the core CSP. No other changes were made in this appendix.
Version 3.1, 31 July 2018
Key amendments and rationale for changes: **Section 2.1 Change to the status of the Module (new):** Information added to summarise observations leading to the decision to stop the clinical development program of vistusertib and, consequently, recruitment to Module 4 which investigates vistusertib in combination with durvalumab. Following a thorough review of the pre-clinical and clinical data across the vistusertib development programme AstraZeneca has decided to discontinue further clinical development of vistusertib. The decision is based on a lack of efficacy from results from all clinical studies on vistusertib to date including 2 randomised comparator trials vs everolimus and discrepancy between preclinical and clinical effect on pathway inhibition despite similar drug exposure questioning any relevance of supporting preclinical data. As a consequence, patients will not be re-allocated to this module and Table 7 (Schedule of Activities for patients who are re-allocated) has been deleted. **Table 1 Schedule of Activities:** Update to the durvalumab ADA sampling schedule in response to a request from the FDA. Sampling is still required pre-dose on Cycle 1 Day 1 and Cycle 2 Day 1, but is now also subsequently required Q12W within the first year and Q24W in the second year of treatment. Addition of a ±7 day window around the study discontinuation and follow-up visits. Removal of WHO/ECOG assessments: these will now only be performed at screening to reduce the burden on sites. **Section 2.3 Background:** Updates to durvalumab background information in light of emerging data. **Figure 2 Flow diagram:** Updated to reflect the addition of Module 5 to the protocol. **Section 5.3.1 Restrictions applicable to durvalumab:** Amended to extend the period patients should not receive live vaccines to 180 days after the last dose of study drug. Updated for consistency across all modules of the study. **Table 3 Prohibited medications:** Updated to align with updated exclusion criteria in the core protocol. **Section 6.2.3 Study drug administration:** Text moved from the module to the core protocol and amended to allow patients to continue receiving treatment with monotherapy if, in the opinion of the treating physician, they are deriving benefit.

Version 2.0, 26 February 2018

Key amendments and rationale for changes:

IND number updated following advice from the FDA to conduct HUDSON under its own IND, which cross references IND 119833.

Table 1 Schedule of activities: Updated to include the requirement for pregnancy tests on day 1 of every cycle, for women of child bearing potential, whilst the patient is on treatment.

Figure 1 Study design: For patients who are re-allocated to a second treatment within HUDSON, the "screening assessments as per schedule of assessments in the treatment specific module" was corrected to state "as per schedule of assessments in the core protocol".

2.2.1 Durvalumab: Background information added in line with the new durvalumab IB Edition 12.

2.2.2.2 Vistusertib data: updated information on the combination of vistusertib with fulvestrant was added in line with the new vistusertib IB Edition 8.

2.2.3 Durvalumab and vistusertib in combination: Additional background information provided to evidence that vistusertib may potentiate the effects of immune checkpoint inhibitors.

Based on observations from other studies exploring the hypothesis of TORC1/2 inhibition, *TSC1* and *TSC2* have been removed as biomarkers of interest in HUDSON:

- **4.1 Overall design**
- **Figure 2 Study flow diagram:** *TSC1* and *TSC2* were deleted
- **5.1 Inclusion criteria:** References to *TSC1* and *TSC2* were deleted.

4.3.1 Justification for durvalumab dose: information added on dose justification in line with the new durvalumab IB Edition 12.

4.3.2 Justification of vistusertib dose:

- Updated the information on the number of patients dosed with vistusertib.
- The BISCAY study (D2615C00001), in which the dose and schedule for vistusertib plus durvalumab is the proposed dose for HUDSON, has confirmed the dose as the RP2D.

5.2 Exclusion criteria: changed to align with the vistusertib IB Edition 8

- Addition of renal exclusion criteria (L-8 and L9)

1 Deletion of exclusion criterion L-5i "Abnormal echocardiogram at baseline (left ventricular ejection fraction [LVEF] <50% and shortening fraction [SF] <15%). Appropriate correction to be used if a multigated (radionuclide) angiogram (MUGA) is performed".

5.3 Lifestyle restrictions:

- Blood donation guidance updated to be in line with the new durvalumab IB Edition 12. Section also revised to 'refer to section 5.3 of the core protocol'.
- Reproduction: Information about reproduction restrictions is included within the core protocol to ensure consistency in reproduction and contraception requirements across each module. Patients will be required to adopt birth control methods (and avoid the donation of sperm) from screening until 6 months after the last dose of study drug.

6.2.3 Study drug administration: Patients allocated to a biomarker matched cohort who, in the opinion of the treating physician would benefit from continued treatment with vistusertib whilst durvalumab is discontinued, may continue treatment with prior approval from the study physician. This text was also added to section **6.6 Dose modification** for clarity.

6.6 Dose modification and discontinuation: Clarification of dose modification and discontinuation rules, including:

- If patients' body weight falls ≤30 kg during the study, (s)he will be withdrawn from the study treatment unless (s)he derives some clinical benefit according to the treating physician. This text was also added to section **6.2.1 Durvalumab preparation and handling** for clarity.
- Management of dose interruptions of durvalumab and vistusertib.

Table 7 Schedule of activities for re-allocation of treatment:

- Updated to include the requirement for pregnancy tests for women of child bearing potential, on day 1 of every cycle, whilst the patient is on treatment.
- Footnote added to clarify that eligibility criteria for both core CSP and this module are applicable.

8.4.5.2 Management of vistusertib-related toxicity and **Table 9 Dose modifications and discontinuation criteria for CTCAE Grade 3/4 haematological toxicities:** Clarification of rules to manage haematological toxicities related to vistusertib, in particular for the management of grade 3-4 febrile neutropenia

10. References: Updated in line with the additional background information provided in sections 2.2.1 and 2.2.3. **Various administrative changes.**

Version 1.0, 05 September 2017
Initial Creation

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

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1. PROTOCOL SUMMARY

1.1 Schedule of Activities (SoA)

The Schedule of Activities (SoA) for the on-treatment period for Module 4 is shown in Table 1 below. For the SoA for the pre-screening and main-screening visits, please refer to the core protocol.

Table 1 Schedule of Activities – Treatment intervention period (Module 4)

	C1 28 days Weeks 1-4		**C2** 28 days Weeks 5-8		**C3** 28 days Weeks 9-12	**C4** 28 days Weeks 13-16	**C5 - etc** All cycles 28 days	**Study drug disc.** (28 days after study drug disc.)	**Safety follow-up** (90 days after study drug disc.)	**Survival follow-up**	**Notes**
Week	**1**	**3**	**5**	**7**	**9**	**13**	**17, 21, 25, 29, etc**				
Cycle day	**1**	**15**	**1**	**15**	**1**	**1**	**1**				
Window (days)	**0**[a]	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±7**	**±7**	**±7**	
Study procedures											
Physical examination	X	X	X	X	X	X	X	X			Section 8.2.2 (core protocol)
Vital signs	X	X	X	X	X	X	X	X			Section 8.2.3 (core protocol)
ECG	X	As clinically indicated									Section 8.2.4 (core protocol)
Concomitant medications	X	X	X	X	X	X	X	X			Section 6.5
Laboratory assessments											
Clinical chemistry	X	X	X	X	X	X	X	X			Section 8.2.1 (core protocol). If screening laboratory assessments are performed within 3 days prior to Day 1 they do not need to be repeated at Day 1
Haematology	X	X	X	X	X	X	X	X			
APTT and INR		As clinically indicated									
TSH, free T_3, and free T_4	X	X	X	X	X	X	X	X			Section 8.2.1 (core protocol)
Urinalysis		As clinically indicated									Section 8.2.1 (core protocol)
Pregnancy test	X		X		X	X	X	X			Section 8.2.1.2 (core protocol)
AE/SAE assessment	X	X	X	X	X	X	X	X	X		Section 8.3 (core protocol)
Study drug administration											
Durvalumab	X		X		X	X	X				See Section 6.2.1

Table 1 Schedule of Activities – Treatment intervention period (Module 4)

	C1 28 days Weeks 1-4		**C2** 28 days Weeks 5-8		**C3** 28 days Weeks 9-12	**C4** 28 days Weeks 13-16	**C5 - etc** All cycles 28 days	**Study drug disc.** (28 days after study drug disc.)	**Safety follow-up** (90 days after study drug disc.)	**Survival follow-up**	**Notes**
Week	**1**	**3**	**5**	**7**	**9**	**13**	**17, 21, 25, 29, etc**				
Cycle day	**1**	**15**	**1**	**15**	**1**	**1**	**1**				
Window (days)	**0[a]**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±7**	**±7**	**±7**	
Vistusertib	X		X		X	X	X				See Section 6.2.2
Drug accountability	X	X	X	X	X	X	X	X			Section 6.2.5
Other assessments											
Blood for ctDNA assessments	X	X	X	X	X	X	X	X			Section 8.8 (core protocol)
Circulating soluble factors (plasma)	X	X	X			X		X			Section 8.8 (core protocol)
Whole blood for gene expression (PaxGene RNA tubes)	X	X	X			X		X			Section 8.8 (core protocol)
PBMCs for flow cytometry (activation by / PD-1 CD8+)	X	X	X			X					Section 8.8 (core protocol)
TCR immune-sequencing	X	X	X			X					Section 8.8 (core protocol)

Table 1 Schedule of Activities – Treatment intervention period (Module 4)

	C1 28 days Weeks 1-4		**C2** 28 days Weeks 5-8		**C3** 28 days Weeks 9-12	**C4** 28 days Weeks 13-16	**C5 - etc** All cycles 28 days	**Study drug disc.** (28 days after study drug disc.)	**Safety follow-up** (90 days after study drug disc.)	**Survival follow-up**	**Notes**
Week	**1**	**3**	**5**	**7**	**9**	**13**	**17, 21, 25, 29, etc**				
Cycle day	**1**	**15**	**1**	**15**	**1**	**1**	**1**				
Window (days)	**0[a]**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±7**	**±7**	**±7**	
Blood sample for ADA for durvalumab (pre-dose except at safety follow up)	X		X				X (C5D1) then Q12W in first year, then Q24W in second year		X		Section 8.5.3 (core protocol)
Tumour evaluation (CT or MRI) (RECIST 1.1)		Every 6 weeks ±1 week for the first 24 weeks relative to the date of first dose (Cycle 1 Day 1), then every 8 weeks ± 1 week thereafter, until objective disease progression as defined by RECIST 1.1 and confirmed with a subsequent scan (in the absence of clinically significant deterioration)									Section 8.1 (core protocol)
Biopsy on-treatment (mandatory)				X							Section 8.8 (core protocol). This should align with the first RECIST assessment.
Biopsy on disease progression (mandatory only for re-allocated patients)								X			Section 8.8 (core protocol)
Subsequent cancer therapy									X	X	Section 8.1.3.1 (core protocol). To be done every 3 months

Table 1 Schedule of Activities – Treatment intervention period (Module 4)

	C1 28 days Weeks 1-4		**C2** 28 days Weeks 5-8		**C3** 28 days Weeks 9-12	**C4** 28 days Weeks 13-16	**C5 - etc** All cycles 28 days	**Study drug disc.** (28 days after study drug disc.)	**Safety follow-up** (90 days after study drug disc.)	**Survival follow-up**	**Notes**
Week	**1**	**3**	**5**	**7**	**9**	**13**	**17, 21, 25, 29, etc**				
Cycle day	**1**	**15**	**1**	**15**	**1**	**1**	**1**				
Window (days)	**0**[a]	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±7**	**±7**	**±7**	
Survival status										X	Section 8.1.3.1 (core protocol). To be done every 3 months

[a] Every effort should be made to minimise the time between allocation to treatment and starting treatment.

Note, if main screening assessments have been performed within 3 days prior to C1D1, then assessments do not need to be performed on C1D1 pre-dose.

ADA Anti-drug antibodies; AE adverse event; APTT activated partial thromboplastin time; C cycle; CD8+ cytotoxic T-cell; CT computed tomography; ctDNA circulating tumour DNA; D day; ECG electrocardiogram; INR international normalised ratio; RECIST Response Evaluation Criteria in Solid Tumours 1.1; MRI magnetic resonance imaging; PBMC peripheral blood mononuclear cell; PD-1 programmed cell death-1; Q12W every 12 weeks; Q24W every 24 weeks; SAE serious adverse event; TCR T-cell receptor repertoire; TSH thyroid-stimulating hormone; T_3 triiodothyronine; T_4 thyroxine.

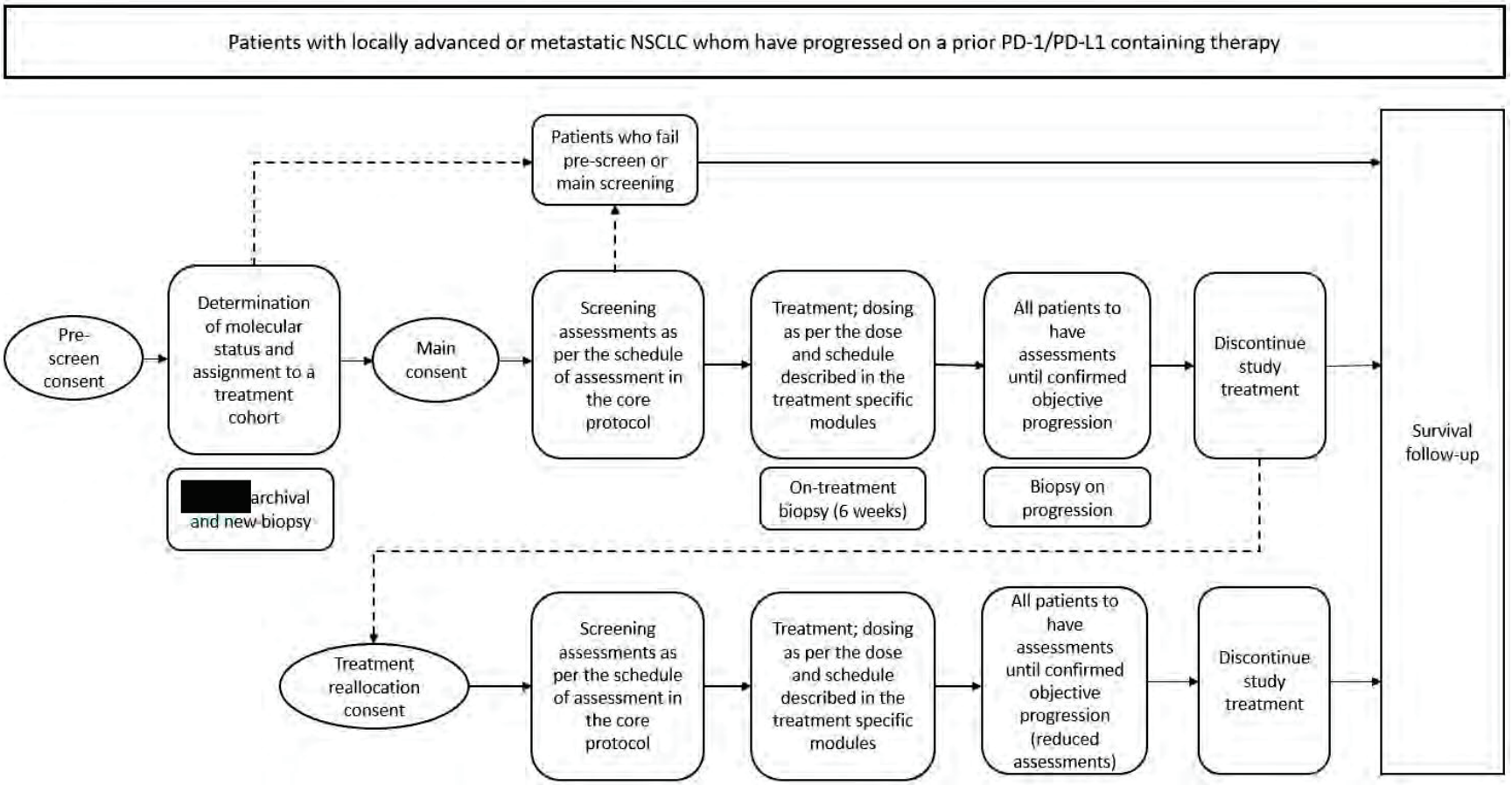
1.2 Synopsis

Please refer to Section 1.2 of the core protocol.

1.3 Schema

The general study design is summarised in Figure 1.

Figure 1 Study design



ctDNA circulating tumour DNA; NSCLC non-small cell lung cancer; PD-1 programmed cell death 1; PD-L1 programmed cell death ligand 1

2. INTRODUCTION

Study D6185C00001 (HUDSON) is a Phase II, open-label, multi-centre umbrella study in patients who have received an anti-programmed cell death-1 (PD-1)/anti-programmed cell death-ligand 1 (PD-L1) containing therapy and a platinum-doublet regimen for locally advanced or metastatic non-small cell lung cancer (NSCLC) either separately or in combination. The patient must have had disease progression on a prior line of anti-PD-1/PD-L1 therapy. The modular design allows the evaluation of the efficacy, safety, and tolerability of multiple study drugs. This module to the core study protocol describes Module 4, which will investigate the efficacy, safety, and tolerability of durvalumab administered in combination with vistusertib in biomarker matched patients (Cohort A.4.RIC).

2.1 Change to status of the module

No further patients will be allocated or consented to receive treatment in Module 4. Going forward, patients who enter pre-screening and whose tumour biopsy shows a RICTOR amplification will be allocated to an alternative treatment cohort within the HUDSON study, either a matched or a non-matched cohort as appropriate based on the patient's molecular profile. Patients already receiving study treatment can either choose to discontinue from study treatment or, where the investigator believes patients are gaining clinical benefit, patients may continue to receive study treatment. The patient should continue attending subsequent study visits and data collection should continue according to the study protocol.

2.1.1 Rationale for the change in status

The decision to discontinue the development of vistusertib is based on a lack of efficacy from results from all studies on vistusertib to date including two randomised comparator trials vs everolimus:

- ZEBRA study in metastatic renal cell cancer (NCT01793636); ZEBRA (EudraCT number 2012-002874-30) was a randomised open-label phase II trial, conducted in patients in the United Kingdom, with advanced or metastatic clear cell renal cell carcinoma comparing oral vistusertib (dual mTORC1/2 inhibitor) 50 mg twice daily versus oral everolimus (mTOR inhibitor) control at the European Union (EU) approved dose of 10 mg once daily. The trial was terminated early following recommendations from the study independent data monitoring committee. Based on an interim analysis of progression free survival (PFS) and overall survival (OS), median PFS and OS were significantly inferior for vistusertib compared with everolimus (PFS 1.8 vs. 4.6 months, hazard ration (HR) 2.8 (95% confidence interval [CI] 1.2-6.5), OS 4.9 months versus not reached, HR 4.3 (95% CI 1.1-16.5). This was despite promising pre-clinical data supporting the hypothesis that combined TORC1 and TORC2 inhibition is more active than isolated TORC1 inhibition and clinical PK concentrations were consistent with the pre-clinical studies (Zheng et al 2015).

- MANTA study in metastatic oestrogen receptor positive (ER+) breast cancer (NCT02216786); MANTA (EudraCT number 2013-002403-34) is a randomised open-label phase II study, conducted in patients across several countries across and outside the EU (including Spain, but not the United States), with ER+ human epidermal growth factor receptor 2 negative (HER2-) metastatic breast cancer, with 4 arms: 1. Vistusertib (50 mg twice daily) in combination with fulvestrant (500 mg intramuscularly monthly); 2. Vistusertib (125 mg twice daily 2 days on/5 days off) in combination with fulvestrant; 3. Everolimus (10 mg once daily; EU approved dose) in combination with fulvestrant; 4. Fulvestrant. The final PFS analyses of this trial were presented at SABCS 2017. Vistusertib in combination with fulvestrant was significantly inferior to everolimus in combination with fulvestrant. Vistusertib in combination with fulvestrant failed to show any statistical PFS benefit over monotherapy fulvestrant. These data were not consistent with preclinical data that suggested that combined TORC1 and TORC2 inhibition is more efficacious than fulvestrant alone.

Following release of the MANTA data AstraZeneca conducted a thorough review of the reasons why vistusertib may not be as clinically effective as everolimus in renal cell cancer and breast cancer, focusing on the extent to which vistusertib down regulates the mTOR pathway preclinically and clinically.

The review indicated that clinically, modulation of the pharmacodynamic markers in tumour biopsies was modest following vistusertib treatment at the recommended phase II dose at continuous schedule (50 mg twice daily). In the phase I, first time in patient, advanced solid tumour study (Basu et al 2015) median changes in phosphorylation of pharmacodynamic biomarkers following vistusertib treatment at 50 mg twice daily were:

- pS6 (mTORC1 biomarker): 49.0% decrease (n=8 paired biopsies)
- p4EBP1 (mTORC1 biomarker): 10.8% increase (n=7 paired biopsies)
- pAKT (mTORC2 biomarker): 33.4 % decrease (n=4 paired biopsies)

An insufficient number of evaluable tumour biopsies were collected in any clinical study at the 125-mg intermittent dose to draw conclusions about this dose in tumour tissue.

Inhibition of phosphorylation of pharmacodynamic markers in blood was observed at the recommended phase II schedules in the phase I monotherapy setting.

- Evaluation of p4EBP1(T37/46) in monocytes after a single dose of study treatment provided evidence of vistusertib-induced TORC1 inhibition. For example, the median percentage change in p4EBP1 at 2 hours after a single dose of vistusertib was -47.4% (n=6, range: -94.3% to 37.3%, negative changes indicate decrease) in the continuous twice daily 50 mg solution dosing group, and -48.5% (n=9, range: -87.7% to -8.9%) in the intermittent twice daily 125 mg tablet dosing group.
- The phosphorylation of AKT (S473) was inhibited in platelet rich plasma, thereby providing evidence for vistusertib-induced TORC2 biomarker inhibition in surrogate

tissue. At 2 hours after a single dose of vistusertib, the median percentage change was -76.2% (n=8, range: -100.0% to 13.5%) in the continuous twice daily 50 mg solution dosing group and -68.3% (n=8, range: -92.1% to -7.0%) in the intermittent twice daily 125 mg tablet dosing group.

However, for the continuous regimen, inhibition of either marker is less than maximum in all patients with recovery towards baseline levels during the dosing interval. While there is slightly higher inhibition following administration of the 125 mg twice daily 2 days on/5 days off intermittent schedule, PK/PD modelling predicts some recovery during dosing and complete recovery to baseline 24 hours after the last dose on Day 2. Maximum inhibition has not been observed even at higher, non-tolerated doses up to 225 mg.

AstraZeneca believe that vistusertib does not inhibit mTORC1 markers as highly as everolimus clinically based on cross trial comparisons from phase I trials with diverse solid tumours (Tabernero et al 2008).

Following this review, we investigated the pharmacodynamics further in an additional on-going phase 1 clinical study of the combination of acalabrutinib (a Bruton's Tyrosine Kinase inhibitor) with vistusertib in diffuse large B-cell lymphoma (DLBCL) (NCT03205046). The pharmacodynamics of vistusertib on TORC1 (p-4EBP1) and TORC2 (p-AKT) biomarkers was evaluated using a flow cytometry based assay from whole blood. In DLBCL patients, peripheral B cells were not often detectable, therefore monocyte and lymphocyte populations were evaluated by flow cytometry. At either dose and schedule (35, 50 mg twice daily continuous or 100, 125 mg twice daily 2 days on 5 days off) reductions in the pharmacodynamic biomarkers were at best 50% pathway inhibition (p-AKT, p-4EBP1) (n=13).

In contrast, when the time course of pharmacodynamic inhibition was investigated further in our pre-clinical models used to support the ER+ breast cancer and DLBCL programmes, almost complete inhibition of pS6, p4EBP1 and pAKT was observed throughout the time course in tumours, despite the exposure of vistusertib being comparable to that observed in patients. This was observed for both the continuous (15 mg/kg once daily) and intermittent schedules (20 mg/kg twice daily) investigated in these models. We estimate that doses appreciably higher than the highest dose investigated in humans, (eg, 225 mg, administered at least twice daily), would be required to achieve comparable inhibition in blood in patients as observed in tumour in our xenograft models. The dose would likely need to be much higher again to achieve comparable pharmacodynamic inhibition in tumours in patients. Given the clinical tolerability profile of vistusertib observed at doses above the current recommended phase IIb regimens, we believe this to be unachievable in a clinical setting.

Based on the current lack of evidence supporting pre-clinical to clinical translation of the doses and schedules used pre-clinically, AstraZeneca no longer has confidence in the clinical

relevance of supporting pre-clinical data. These data lead us to conclude that without further data, the efficacy findings in ZEBRA and MANTA are considered relevant to other indications.

2.2 Study rationale

As described in Section 2.2 of the core protocol, immune checkpoint inhibitors targeting the PD-1/PD-L1 pathway have shown significant activity in the first- and second-line treatment settings in patients with NSCLC. However, it is becoming evident that there is a new and significant patient population emerging that does not respond to anti-PD-1/PD-L1 containing therapy (primary resistance) or progresses during anti-PD-1/PD-L1 containing therapy (acquired resistance). There is currently no established therapy for patients who have developed resistance to PD-1/PD-L1 and platinum-doublet therapies, and novel treatments for these patients are urgently needed.

The aim of this umbrella study (D6185C00001) is to investigate multiple study drugs for the treatment of NSCLC in molecularly matched and non-matched patient populations after failure of immune checkpoint inhibitors, to identify patient populations who may respond favourably to novel anti-tumour therapies.

2.3 Background

Durvalumab is currently in clinical development as an anti-cancer therapy in a variety of malignancies. Durvalumab is United States (US) Food and Drug Administration (FDA) approved in bladder urothelial carcinoma and for the treatment of patients with stage III NSCLC whose tumours are not able to be surgically removed (unresectable) and whose cancer has not progressed after treatment with chemotherapy and radiation (chemoradiation), (IMFINZI™ US Prescribing Information). Development of vistusertib has been discontinued.

This Module 4 will investigate both agents in combination, to test the hypothesis that the combination will result in complementary anti-tumour activity. Brief background on durvalumab and vistusertib, including their mechanisms of action, is provided below. For detailed descriptions of the chemistry, pharmacology, efficacy, and safety of durvalumab and vistusertib, please refer to the respective Investigator's Brochures.

The study will recruit biomarker matched patients (see Section 4.1). Patients with amplifications in the rapamycin-insensitive companion of mTOR (*RICTOR*) may be allocated to this cohort (see Section 4.2). In tumour cells with *RICTOR* amplification, intermittent dosing of vistusertib (AZD2014) is expected to cause profound cell cycle arrest and apoptosis (Cheng et al 2015) and tumour-specific T-cell infiltrates (Jiang et al 2011). Immune checkpoint blockade by durvalumab at the same time is expected to overcome the inhibitory action of PD-L1, promoting activation of T-cells at the tumour site.

2.3.1 Durvalumab

2.3.1.1 Overview of durvalumab

Expression of PD-L1 protein is an adaptive immune response that helps tumours evade detection and elimination by the immune system. PD-L1 can be induced by inflammatory signals (eg, interferon-gamma) and can be expressed on both tumour cells and tumour-associated immune cells in tumour microenvironment. PD-L1 blocks T-cell function and activation through interaction with PD-1 and CD80 (B7.1). By binding to its receptors, PD-L1 reduces cytotoxic T-cell activity, proliferation, and cytokine production. Durvalumab is a fully human, high affinity, immunoglobulin G1 kappa monoclonal antibody that selectively blocks the interaction of PD-L1 with PD-1 and cluster of differentiation (CD)80 (B7.1) while leaving PD-1/ programmed cell death ligand-2 interaction intact. Durvalumab does not induce antibody dependent cell-mediated cytotoxicity. Selective blockade of PD-L1/PD-1 and PD-L1/CD80 interactions enhances antitumour immune responses. These antitumour responses may result in tumour elimination.

Durvalumab is approved in a number of territories including the US, EU, Japan, Canada and Brazil under the brand name IMFINZI™ Injection.

The recommended dose as per the IMFINZI package insert is 10 mg/kg administered as an IV infusion over 60 minutes Q2W.

For more information, please refer to the latest version of the Durvalumab Investigator's Brochure.

2.3.1.2 Durvalumab data

To date, durvalumab has been given to more than 6000 patients as part of ongoing studies either as monotherapy or in combination with other anticancer agents. Details on the safety profile of durvalumab monotherapy are summarized below. Refer to the current durvalumab IB for a complete summary of pre-clinical and clinical information including safety, efficacy, and pharmacokinetics (PK).

Clinical activity in locally advanced NSCLC

double-blind, placebo-controlled, multicentre study in 713 patients with histologically or cytologically confirmed locally advanced, unresectable NSCLC. Patients had completed definitive platinum-based chemoradiation within 1 to 42 days prior to initiation of the study and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Ninety-three percent of patients had received a total dose of 54 to 66 Gy of radiation. The study excluded patients who had progressed following concurrent chemoradiation therapy, patients with active or prior documented autoimmune disease within 2 years of initiation of the study; a history of immunodeficiency; a history of severe immune-mediated adverse reactions; medical conditions that required systemic immunosuppression, except physiological

dose of systemic corticosteroids; active tuberculosis or hepatitis B or C or HIV infection or patients receiving live attenuated vaccine within 30 days before or after the start of durvalumab. Patients were randomised 2:1 to receive 10 mg/kg durvalumab (n=476) or 10 mg/kg placebo (n=237) via IV infusion every 2 weeks (Q2W) for up to 12 months or until unacceptable toxicity or confirmed disease progression. Randomisation was stratified by gender, age (<65 years vs. ≥65 years) and smoking status (smoker vs. nonsmoker). Patients with disease control at 12 months were given the option to be re-treated upon disease progression. Tumour assessments were conducted every 8 weeks for the first 12 months and then every 12 weeks thereafter.

The demographics and baseline disease characteristics were well balanced between study arms. Baseline demographics of the overall study population were as follows: male (70%), age ≥65 years (45%), White (69%), Asian (27%), other (4%), current smoker (16%), past-smoker (75%), and never smoker (9%), World Health Organisation (WHO)/ECOG PS 0 (49%), WHO/ECOG PS 1 (50%). Disease characteristics were as follows: Stage IIIA (54%), Stage IIIB (44%), histological subgroups of squamous (47%), non-squamous (53%), PD-L1 expression in tumour cells (TC)≥25% (22%), PD-L1 expression TC<25% (41%). (PD-L1 status was retrospectively analysed using the Ventana PD-L1 [SP263] Assay in 451 patients with available samples, taken prior to concurrent chemoradiation therapy).

At the time of the interim progression-free survival (PFS) analysis, the median PFS by blinded independent central review (BICR) was significantly longer with durvalumab treatment (16.8 months) compared with placebo (5.6 months); hazard ratio 0.52; 98.9% CI: 0.39, 0.70; p<0.0001. At the time of the interim overall survival (OS) analysis, the median OS was not reached for the durvalumab arm and was 28.7 months for the placebo arm; stratified hazard ratio for death, 0.68; 99.73% CI, 0.469, 0.997; p=0.0025). The 24-month OS rate was 66.3% with durvalumab vs 55.6% with placebo.

Clinical activity in recurrent and metastatic NSCLC

Based on current data from the ongoing Study CD ON MEDI4736-1108 (NCT01693562), evidence of clinical activity with durvalumab has been observed. The following responses were observed in patients with NSCLC.

Overall, clinical activity was observed in both the PD-L1 high (defined as having tumour cells [TC] ≥25%) and PD-L1 low/negative (defined as TC <25%) subgroups, however, patients with PD-L1 high tumours had higher objective response rates (ORRs).

The ORR per BICR was 21.8% and 6.4% in patients with PD-L1 high and low/negative tumours, respectively and 15.3% in the overall population regardless of PD-L1 expression. The ORR was 25.9%, 14.3% and 11.5% in the 1L, 2L and 3L+ cohorts, respectively. Median duration of response (DOR) was 17.74 months. Median OS was 12.4 months; median OS was

21.0, 11.8 and 9.3 months in the 1L, 2L and 3L+ cohorts, respectively. The OS rate at 24 months was 29.6%.

The ATLANTIC study in third-line or higher NSCLC showed higher ORR and survival outcomes in high PD-L1 positive patients. Across cohorts the ORR ranged from 3 to 43%, median progression-free survival (PFS) ranged from 1.8 to 5.5 months and median OS ranged from 5.9 to 13.6 months but was not reached at the time of initial reporting in the >90% PD-L1 expressors. The ORR and survival outcomes reported in durvalumab studies are in keeping with other similar agents targeting the PD-1/PD-L1 axis (Garassino et al 2017).

-oncology agents targeting the PD-1/PD-L1 pathway have demonstrated activity as monotherapy and in combination with chemotherapy in patients who are immunotherapy-naïve. However, the present study will recruit patients who either have primary resistance to anti-PD-1/PD-L1 therapy or who developed acquired resistance while on anti-PD-1/PD-L1 therapy. Thus, in this immunotherapy-resistant setting, durvalumab will be administered in combination with an agent that has a different and complementary mechanism of action in order to maximise the likelihood of clinical activity.

2.3.2 Vistusertib

2.3.2.1 Overview of vistusertib

Vistusertib is a selective inhibitor of the kinase activity of mammalian target of rapamycin (mTOR) serine threonine kinase, which plays a critical role in regulating cellular energy sensing, growth and metabolism. Vistusertib inhibits the proliferation of a range of cell lines derived from solid and haematological tumours. Vistusertib shows dose dependent pharmacodynamic and anti-tumour activity in preclinical in vivo mouse models at well tolerated doses. Vistusertib inhibits downstream targets of both mTORC1 and mTORC2 in a dose- and time-dependent manner. By inhibiting both mTOR complexes, vistusertib may offer therapeutic advantages over rapalogues that selectively inhibit mTORC1 alone.

2.3.2.2 Vistusertib data

Monotherapy

In the monotherapy study (D2270C00001) at the 50 mg twice daily (BD) dosed continuously in a total of 40 patients, 2 patients had an objective response; 1 patient with pancreatic acinar cell type cancer and 1 patient with ER+ breast cancer had confirmed partial responses (PR) according to Response Evaluation Criteria In Solid Tumours (RECIST) version 1.1, and received vistusertib treatment for 175 and 206 days, respectively. In addition, 12 patients in the 50 mg BD group, and 4 patients each in the 100 mg QD and 125 mg intermittent cohort achieved stable disease (SD).

Combination with fulvestrant in patients with metastatic breast cancer

For the combination study with fulvestrant (D2270C00005) information on the best objective responses in all patients and patients with measurable disease at baseline, is included in the vistusertib Investigator's Brochure.

Combination therapy of vistusertib with fulvestrant has demonstrated encouraging response rate data at MTDs of both continuous and intermittent dosing schedules in a Phase I setting. In Study D2270C00005 (breast cancer), there were partial (confirmed and unconfirmed) responses at every MTD dose group: for the 50 mg BD continuous dosing group, unconfirmed PR 3/11 (27.3%), confirmed PR 2/11 (18.2%); for the 125 mg BD intermittent dosing group, unconfirmed PR 3/20 (15.0%), confirmed PR of 1/20 (5.0%).

Key preliminary efficacy data for ongoing AZ sponsored studies and ESR studies are as follows: as of 5th October 2017, there was no efficacy data available for ongoing AZ sponsored Study D2270C00020 (PASTOR). The MANTA (breast cancer) and ZEBRA (renal cell cancer) studies did not meet the primary endpoint for vistusertib compared with everolimus. Data from MANTA showed that there were differences between the intermittent and continuous dosing schedules, with a lower rate of rash or stomatitis but a higher rate of nausea/vomiting in the intermittent dosing schedule.

Vistusertib safety findings

In the Phase I study (DC2270C0001), the overall safety findings for vistusertib monotherapy dosed continuously are consistent with AEs already reported for other mTOR inhibitors: rash, pruritus, mucositis, fatigue, nausea, vomiting, diarrhoea, constipation, pneumonitis, and decreased appetite. However, at intermittent dosing schedules, vistusertib shows a different safety profile compared to continuous dosing schedules. At intermittent dosing schedules (125 mg BD 2 days on and 5 days off) the main AEs reported were nausea and vomiting, which also led to dose discontinuation in 1 patient. There was a reduction in rash at intermittent dosing schedules (from 69.2% to 16.2% in combination and 48.8% to 15.4% in monotherapy), pruritus (61.5% to 13.5% in combination and 34.1% to 0% in monotherapy) and mucositis (from 69.2% to 29.7% in combination therapy and 43.9% to 30.8% in monotherapy). Interestingly, there were no cases of pneumonitis observed with this intermittent monotherapy schedule (compared with 2.4% and 7.7% in the continuous monotherapy and combination therapies respectively). Given the small number of patients treated with the continuous regimen in non-randomised trials, no final conclusions can be made. Nevertheless, the intermittent dosing schedules, showing similar efficacy at least in combination with fulvestrant, offer an important new development option for an mTOR kinase inhibitor with a potentially better tolerated safety profile, especially for combinations with other agents.

In a Phase IIa, multi-centre, single-arm trial D2274C00001 (STORK [NCT02038322]) exploring the combination of vistusertib and weekly paclitaxel in patients with relapsed or refractory NSCLC after at least one line of prior therapy, patients received a single weekly paclitaxel infusion of 80 mg/m^2 on Day 1 of each week, and 50 mg BD vistusertib on the first 3 days of each week for 6 weeks. After review of preliminary, unvalidated safety and efficacy data from 11 patients, who typically had a large number of comorbidities, suggested that the vistusertib with weekly paclitaxel at this dose level did not appear to be an acceptable regimen in this patient population because of discontinuations due to rapid disease progression and/or AEs. However, the same combination (at same the dose level) explored in STORK is still investigated in other disease types and also at a lower dose level of 25 mg BD (3 days on and 4 days off) of vistusertib in relapsed/refractory NSCLC patients in externally sponsored research studies (ESRs).

In a Phase I, open-label, multicentre trial D2270C00008 to assess the safety, tolerability, PK, and preliminary efficacy of vistusertib in Japanese patients with solid malignancies, dose levels of 50 mg continuous BD dosing (Cohort 1), and 125 mg intermittent BD dosing (Days 1 and 2 days on/5 days off) (Cohort 2) for monotherapy treatment, and 25 mg or 50 mg continuous BD intermittent (3 days on/4 days off) in combination with paclitaxel (in indications except sqNSCLC) (Cohorts 3-1 and 3-2) were explored. All 27 (100%) patients reported at least 1 AE, and 26 (96.3%) patients had at least 1 AE considered by the Investigator to be causally related to the study treatment. The most commonly reported AEs were nausea (13 [48.1%] patients), neutrophil count decreased (10 [37.0%] patients), rash (9 [33.3%] patients), and pyrexia (9 [33.3%] patients), with nausea being the most commonly reported AE considered to be related. Adverse events of CTCAE Grade ≥3 were reported by 11 (40.7%) patients of whom 8 (29.6%) were considered by the Investigator to be causally related to the study treatment. The most commonly reported AE of CTCAE Grade ≥3 was neutrophil count decreased (6 [22.2%] patients) (Cohort 1 [vistusertib 50 mg BD continuous dosing] had no reported neutrophil count decreased AE of CTCAE Grade ≥3).

No AEs with an outcome of death were reported during the study, up to the time of data cut off. Serious adverse events were reported by 8 (29.6%) patients of whom 4 (14.8%) patients had SAEs considered by the Investigator to be causally related to the study treatment (pyrexia, diarrhoea, herpes zoster, and nausea).

Overall 4 (14.3%) patients had AEs that led to the discontinuation of vistusertib. One AE of Grade 2 rash that led to discontinuation was considered vistusertib-related.

Preliminary safety data up to cut-off date of 31 March 2018 is available from the ongoing Phase I/II multicentre Study D2270C00020 (PASTOR) that is investigating the combination of vistusertib and palbociclib on a background of hormonal therapy in patients with locally advanced/metastatic ER+ breast cancer. All patients in the study experienced an AE, and the

majority of patients had AEs that were considered related to vistusertib (96.3%). The most common AEs related to study treatment reported in ≥20% patients overall were neutropenia (31/54 [57.4%] patients), fatigue (25/54 [46.3%] patients), nausea (24/54 [44.4%] patients), diarrhoea (20/54 [37.0%] patients), rash (17/54 [31.5%] patients), anaemia (13/54 [24.1%] patients), and mucositis (13/54 [24.1%] patients).

SAE MedDRA terms reported in >1 patient overall were neutropenia (3/54 [5.6%] patients) and infections (2/54 [3.7%] patients). Overall, 2 patients experienced SAEs that were considered to be causally related to vistusertib (rash and neutropenia in 1 patient, neutropenia in 1 patient).

There were no deaths in this study. Two patients overall had AEs leading to discontinuation of vistusertib; rash (1/54 [1.9%]) and vitreous haemorrhage (1/54 [1.9%]). Safety data from ESR studies are consistent with the known safety profile of vistusertib.

2.3.3 Durvalumab and vistusertib in combination

A recent publication from Lastwika et al (2016) suggests that the activation of the mTOR pathway tightly regulates PD-L1 expression in lung adenocarcinomas. The authors conclude that activation of the mTOR pathway promotes immune escape and confirmed the efficacy of an mTORi with a PD-1 antibody in a lung syngeneic mouse model. Our in-house data at AstraZeneca confirms that vistusertib may potentiate the effects of immune checkpoint inhibitors. In the MC38 and CT26 models (mouse syngeneic colorectal cancer) vistusertib (AZD2014) alone did not impact tumour growth as expected but there was immune potentiation in combination with anti-CTLA4 (αCTLA4) checkpoint blockade (submitted, PNAS, Langdon et al). Underlying these anti-tumour effects, mTORC1/2 inhibition promoted pro-inflammatory cytokine production by antigen presenting cells and conferred a greater survival potential to effector CD8 T-cells, specifically under conditions where their activation was suboptimal (Langdon et al). There are a number of recent publications that support the rationale for combining mTOR and immune checkpoint inhibitors (Pedicord VA et al 2015; Hirayama Y et al 2016; Moore EC et al 2016; Beziaud L et al 2009, Mannick et al 2014, Araki K et al 2009). Together these data provide a clear rationale to investigate vistusertib/immune checkpoint inhibitor combinations in the clinic. Notably there are two open clinical trials exploring everolimus and vistusertib in combination with immune checkpoint inhibitors (NCT02890069, NCT02546661).

There are no established or approved biomarkers to enrich for response to mTOR inhibitors. *RICTOR* amplification is a potential candidate but there are no available clinical data from prospective clinical trials that have assessed the clinical activity of mTOR inhibitors in these settings.

Rapamycin-insensitive companion of mTOR (RICTOR) is a protein that forms part of the mTORC2 complex and the hypothesis is that *RICTOR* amplification may hyperactivate TOR kinase activity. Therefore, we propose to test this hypothesis using vistusertib, a direct TOR kinase inhibitor. Rapalogues, such as everolimus, will not be active in this setting because they indirectly inhibit only the mTORC1 complex. Recent preclinical and clinical data support the rationale for treating *RICTOR* amplified NSCLC patients with vistusertib (Cheng et al 2015).

This module in Study D6185C00001 (Module 4) is for a combination therapy of durvalumab plus vistusertib. Module 4 will investigate the safety, tolerability, and anti-tumour activity of vistusertib in combination with durvalumab in Cohort A.4.RIC, patients matched to the *RICTOR* biomarker. In tumour cells with *RICTOR* amplification, intermittent dosing of vistusertib is expected to cause profound cell cycle arrest and apoptosis (Cheng et al 2015) and tumour specific T-cell infiltrates (Hirayama Y et al 2016). Immune checkpoint blockade by durvalumab at the same time is expected to overcome the inhibitory action of PD-L1 ligand, promoting anti-tumour immunity, including tumour infiltration and activation of T-cells.

2.4 Benefit/risk assessment

As described in Section 2.3 of the core protocol, patients recruited to this study are not expected to have other treatment options apart from monotherapy chemotherapy, such as docetaxel. The survival outcome and toxicity profile of chemotherapy in this setting mean that other active therapies are highly desirable and present a potential advantage for patients.

Whilst patients are able to continue on treatment with vistusertib at the Investigator's discretion, AstraZeneca have discontinued vistusertib development on the grounds of a lack of efficacy compared to everolimus. Evaluation of the safety profiles of durvalumab and vistusertib revealed that there is limited potential for potentiation of the known adverse drug reactions of both agents, due to the different pharmacological mechanisms of action. Management of shared toxicities of vistusertib and durvalumab is described in Section 8.4.5.3. Additionally, several measures, including project-specific safety related inclusion/exclusion criteria, physical examinations, evaluation of AEs/serious adverse events (SAEs) and laboratory testing throughout the study and study treatment modifications and toxicity management guidelines have been incorporated into this study protocol to mitigate any potential or identified risks associated with these agents.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of vistusertib and durvalumab can be found in the respective Investigator's Brochure.

3. OBJECTIVES AND ENDPOINTS

Please refer to the core protocol.

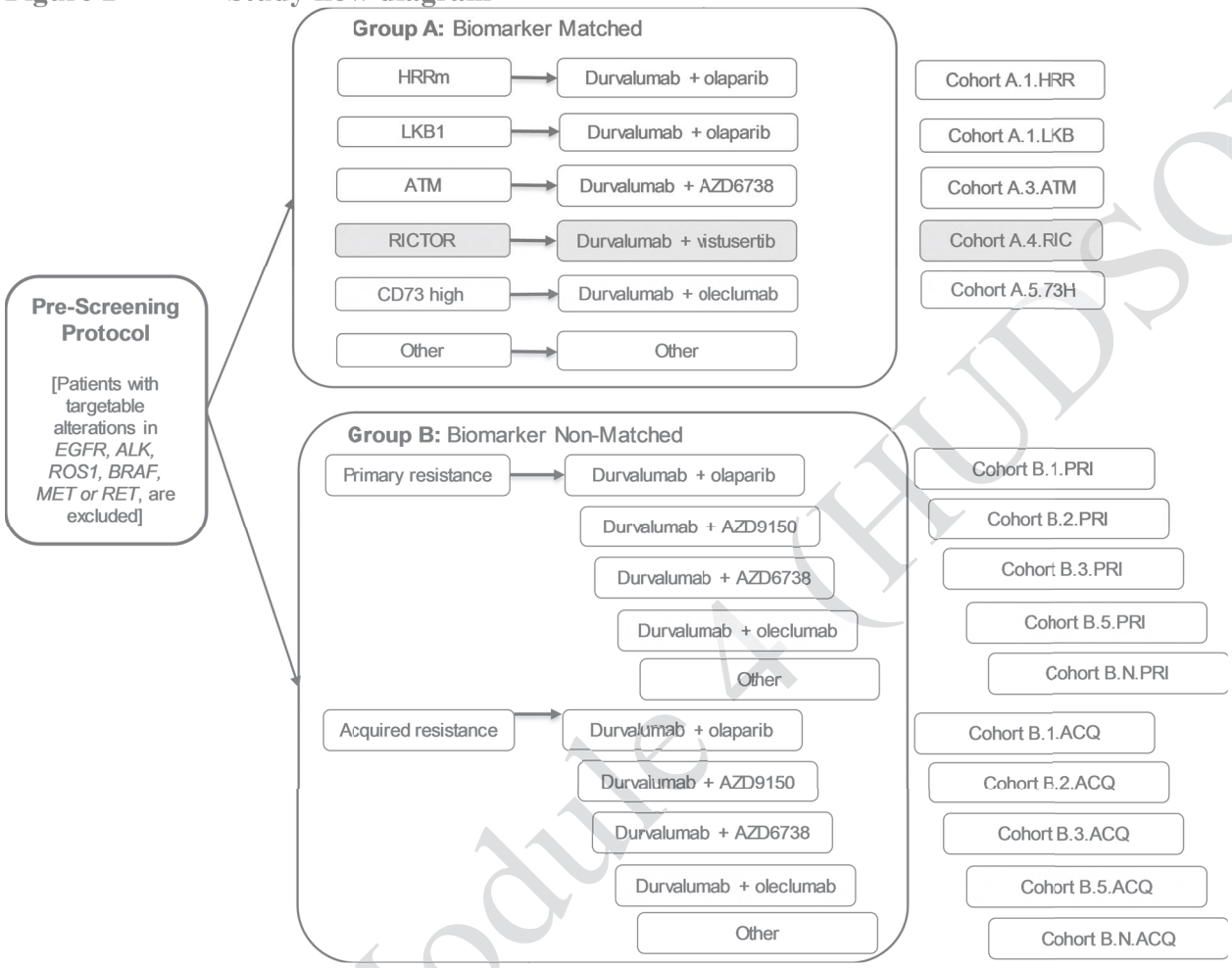
4. STUDY DESIGN

4.1 Overall design

This is an open-label, multi-centre, umbrella study in patients who have received an anti-PD-1/PD-L1 containing therapy and a platinum-doublet regimen for locally advanced or metastatic NSCLC either separately or in combination. The patient must have had disease progression on a prior line of anti-PD-1/PD-L1 therapy. For an overview of the study design see Figure 2; further details on the overall design are provided in Section 4 of the core protocol. For details on the study treatments given in Module 4, see Section 6.1.

- **Cohort A.4.RIC** will investigate the efficacy, safety, and tolerability of durvalumab given IV at 1500 mg every 4 weeks (Q4W) ±2 days in combination with vistusertib given orally at a dose of 125 mg BD on an intermittent dosing schedule of 2 days on, 5 days off in patients with detectable genetic amplifications in *RICTOR*.
- A study flow diagram is provided in Figure 2. The treatment cohorts described in this module are highlighted in grey

Figure 2 Study flow diagram



Note, Module 4 is closed to recruitment from CSP version 3.0.
ACQ patients with acquired resistance; *ATM* ataxia telangiectasia mutated; *HRRm* mutation detected in a homologous recombination repair gene; *LKB1* liver kinase B1; PRI patients with primary resistance; *RICTOR* rapamycin-insensitive companion of mechanistic target of rapamycin (mTOR) complex.

4.2 Scientific rationale for study design

The modular design of this study allows evaluation of the efficacy, safety, and tolerability of multiple study drugs. Owing to the different schedules and routes of administration of the study drugs, the study requires an open-label design.

Mammalian target of rapamycin is a serine/threonine kinase that belongs to the super-family of phosphatidylinositol-3 kinase (PI3K) related kinases (PIKKs). The highly-conserved TOR kinase is known to be a central regulator of cell growth and metabolism in response to nutrient availability. The TOR forms the catalytic core of at least two functionally distinct complexes, TOR complex 1 (TORC1) and TOR complex 2 (TORC2). These complexes contain shared and distinct partner proteins and control a number of cellular processes in response to diverse environmental cues. Vistusertib targets the catalytic function of mTOR, thereby inhibiting both mTORC1 and mTORC2. This causes profound cell cycle arrest and apoptosis in a number of different tumour types.

Molecular classification of lung cancer has uncovered amplifications in rapamycin-insensitive companion of mTOR (RICTOR). RICTOR up-regulation strengthens mTORC2 activity, which in turn promotes cell growth and motility. Conversely, RICTOR down-regulation or pharmacological inhibition of mTORC2 suppresses cell proliferation and tumour formation (Cheng et al 2015). The dose, temporal sequencing of administration and the impact of mTOR inhibition on different immune cell types may play a key role in the type of immune response seen. Recent evidence has shown that treatment with mTOR inhibitors increases tumour-specific T-cell infiltrates and delivers anti-tumour activity in mouse syngeneic graft models (Hirayama et al 2016). Clinical data support the immunostimulatory potential of short-term, low-dose administration of mTOR inhibitors: in a study of elderly volunteers, 6 weeks of everolimus before influenza immunisation enhanced the vaccine response and decreased the percentage of peripheral CD4+ and CD8+ T-cells expressing PD-1 (Langdon et al, submitted publication; Lastwika et al 2016; Mannick et al 2014) whereas low dose, chronic daily treatment with mTOR inhibitors is used to induce immunosuppression and prevent graft rejection.

4.3 Justification for dose

4.3.1 Justification for durvalumab dose

A durvalumab dose of 20 mg/kg Q4W is supported by in vitro data, pre-clinical activity, clinical PK/pharmacodynamics, biomarkers, and activity data from Study CD-ON-MEDI4736-1108 (hereafter referred to as Study 1108) in patients with advanced solid tumors and from a Phase I study performed in Japanese patients with advanced solid tumor (D4190C00002).

PK/Pharmacodynamic data

Based on available PK/pharmacodynamic data from ongoing Study 1108 with doses ranging from 0.1 to 10 mg/kg Q4W or 15 mg/kg Q4W, durvalumab exhibited non-linear (dose dependent) PK consistent with target-mediated drug disposition. The PK approached linearity at ≥3 mg/kg Q4W, suggesting near complete target saturation (membrane-bound and sPD-L1), and further shows that the durvalumab dosing frequency can be adapted to a particular regimen given the linearity seen at doses higher than 3 mg/kg. The expected half life with doses ≥3 mg/kg Q4W is approximately 21 days. A dose-dependent suppression in peripheral sPD-L1 was observed over the dose range studied, consistent with engagement of durvalumab with PD-L1. A low level of immunogenicity has been observed. No patients have experienced immune-complex disease following exposure to durvalumab. (For further information on immunogenicity, please see the current durvalumab IB).

A population PK model was developed using the data from Study 1108 (doses=0.1 to 10 mg/kg Q2W or 15 mg/kg Q4W; Fairman et al 2014). Multiple simulations indicate that a similar overall exposure is expected following both 10 mg/kg Q4W and 20 mg/kg Q4W regimens, as represented by AUCss (4 weeks). Median Cmax,ss is expected to be higher with 20 mg/kg Q4W (~1.5 fold) and median Ctrough,ss is expected to be higher with 10 mg/kg Q4W (~1.25 fold). Clinical activity with the 20 mg/kg Q4W dosing regimen is anticipated to be consistent with 10 mg/kg Q4W with the proposed similar dose of 20 mg/kg Q4W expected to (a) achieve complete target saturation in majority of patients; (b) account for anticipated variability in PK, pharmacodynamics, and clinical activity in diverse cancer populations; (c) maintain sufficient PK exposure in case of ADA impact; and (d) achieve PK exposure that yielded maximal antitumor activity in animal models.

Given the similar area under the serum drug concentration-time curve (AUC) and modest differences in median peak and trough levels at steady state, the observation that both regimens maintain complete sPD-L1 suppression at trough, and the available clinical data, the 20 mg/kg Q4W and 10 mg/kg Q4W regimens are expected to have similar efficacy and safety profiles, supporting further development with a dose of 20 mg/kg Q4W.

Clinical data

Refer to the current durvalumab IB for a complete summary of clinical information including safety, efficacy, and PK at the 20 mg/kg Q4W regimen.

Rationale for fixed dosing

A population PK model was developed for durvalumab using monotherapy data Study 1108 (N=292; doses= 0.1 to 10 mg/kg Q4W or 15 mg/kg Q4W; solid tumors). Population PK analysis indicated only minor impact of body weight on the PK of durvalumab (coefficient of

≤0.5). The impact of body weight-based (10 mg/kg Q4W) and fixed dosing (750 mg Q4W) of durvalumab was evaluated by comparing predicted steady state PK concentrations (5th, median, and 95th percentiles) using the population PK model. A fixed dose of 750 mg was selected to approximate 10 mg/kg (based on median body weight of ~75 kg). A total of 1000 patients were simulated using body weight distribution of 40 to 120 kg. Simulation results demonstrate that body weight-based and fixed dosing regimens yield similar median steady state PK concentrations with slightly less overall between-patient variability with fixed dosing regimen.

Similar findings have been reported by others (Narwal et al 2013, Ng et al 2006, Wang et al 2009, Zhang et al 2012). Wang and colleagues investigated 12 monoclonal antibodies and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies (Wang et al 2009). In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-patient variability in PK/pharmacodynamic parameters (Zhang et al 2012).

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar PK exposure and variability, AstraZeneca considered it feasible to switch to fixed dosing regimens. Based on average body weight of 75 kg, a fixed dose of 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) is included in the current study.

Thus, the clinical activity observed coupled with the safety profile, translational science correlates, and non-clinical data supports further development with a dose of 1500 mg Q4W. The dose of durvalumab will not be modified during the study.

4.3.2 Justification for vistusertib dose

The pharmacokinetics of vistusertib have been studied following single and repeat administration of a solution and tablet formulation in cancer patients. Once daily (QD), BD and intermittent dosing (2 consecutive days, 2 days on, 5 days off) have been investigated. In summary, vistusertib is orally available, rapidly absorbed when administered as a tablet and has a short terminal half-life. There is a greater than dose proportional increase in exposure (area under the curve [AUC]) to vistusertib across the dose range investigated with a corresponding decrease in oral clearance (CL/F). At higher doses (>100 mg) the apparent clearance decreases (CL_{ss}/F <CL/F for the same dose) following repeat dosing, with a corresponding increase in terminal half-life. The mechanism for this and clinical relevance has not been fully elucidated.

Absorption of vistusertib is delayed following administration with food (delayed time to reach maximum plasma concentration [T_{max}] and reduction in maximum plasma concentration [C_{max}]) relative to the fasted state, but the extent of exposure (AUC) appears comparable.

Vistusertib is a substrate and weak inhibitor of various cytochrome P450 isoenzymes and drug transporters in vitro. In addition, vistusertib is a weak inducer of cytochrome P450 3A4 (CYP3A4) in vitro. The clinical relevance of these findings has not been fully evaluated. There are specific exclusion criteria and co-medication guidance in place to avoid potential PK drug interactions (see Sections 5.2 and 6.5 of this document).

Considering emerging PK data from ongoing studies, there is no evidence to indicate any ethnic sensitivity in Asian patients compared to Western patients.

As of 05 October 2018, a total of 390 patients have received at least 1 dose of vistusertib in 9 AZ-sponsored studies (152 patients as monotherapy and 238 patients as combination therapy) and 760 in 22 externally-sponsored research (ESR) studies in several indications including breast cancer, solid tumours and squamous non-small cell lung cancer (sqNSCLC).

The vistusertib plus durvalumab combination is being studied in one of the arms of study D2615C00001 (BISCAY). BISCAY is an Open-Label, Randomised, Multi-Drug, Biomarker-Directed, Multi-Centre, Multi-arm Phase 1b Study in patients with Muscle Invasive Bladder Cancer (MIBC) who have progressed on prior treatment. This study will evaluate the safety, tolerability, pharmacokinetics and anti-tumour activity of novel anti-cancer agents as monotherapy and in combination.

Assessment of vistusertib and durvalumab safety profiles prior to the start of BISCAY revealed that there is limited potential for potentiation of the known adverse drug reactions of both agents, due to the different pharmacological mechanisms of action. The two agents have some ADRs in common, eg, diarrhoea, rash, pneumonitis, fatigue and hepatic toxicity, and there is a potential for an increased risk of these overlapping toxicities.

In BISCAY patients received vistusertib 125mg BD orally on an intermittent schedule (2 days on, 5 days off) (the recommended phase 2 dose in monotherapy and in combination with fulvestrant) in combination with durvalumab 1500 mg Q4W. After the first 6 patients had completed 28 days of dosing a safety review committee reviewed the emerging data and agreed to continue with the current dose in the expansion phase To date, vistusertib plus durvalumab has been evaluated in 29 patients in BISCAY.

Based on information to date, the combination of vistusertib and durvalumab is well tolerated in the majority of cases, and no new safety signals have been observed.

Details of all vistusertib studies are summarised in the Investigator's Brochure.

4.4 End of study definition

Please refer to the core protocol.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study in order to assigned/randomised to a study cohort. Under no circumstances can there be exceptions to this rule. Patients who do not meet the entry requirements are screen failures; refer to Section 5.4 of the core protocol.

5.1 Inclusion criteria (Module 4-specific)

Please refer to the Section 5.1 of the core protocol for the inclusion criteria applicable to all modules in the study. Additional inclusion criterion applicable to Module 4 are described below:

L-1. Patients must fulfil all the core eligibility criteria.

L-2. Identification of molecular aberrations:

- Cohort A.4.RIC: detectable genetic amplifications in *RICTOR*.

5.2 Exclusion criteria (Module 4-specific)

Patients must not enter Module 4 of the study if any of the following exclusion criteria apply. Refer to Section 5.2 of the core protocol for the exclusion criteria applicable to all modules in the study. Additional exclusion criteria applicable to Module 4 only are described below:

Prior/concomitant treatment

L-1 Minor surgery (excluding tumour biopsies) within 14 days of first dose of study treatment.

L-2 Exposure to specific substrates of the drug transporters organic anion-transporting protein (OATP)1B1, OATP1B3, multi-drug and toxin extrusion protein (MATE)1 and MATE2K within the appropriate washout period (a minimum of 5 × reported elimination half-life) before the first dose of study treatment. Exposure to strong or moderate inhibitors of inducers of CYP3A4/5, P-glycoprotein (P-gp) (multidrug resistance protein 1 [MDR1]) and breast cancer resistance protein (BCRP) if taken within the stated washout periods before the first dose of study treatment.

L-3 Any haemopoietic growth factors (eg, filgrastim [granulocyte colony-stimulating factor; G-CSF], sargramostim [granulocyte-macrophage colony-stimulating factor; GM-CSF]) within 14 days prior to receiving study treatment (see Section 6.5).

L-4 Prior treatment with other mTOR inhibitors.

2 **Diagnostic assessment**

L-5 Patients who have undergone any of the following procedures or experienced conditions currently or in the preceding 6 months:

(a) Coronary artery bypass graft

(b) Angioplasty

(c) Vascular stent

(d) Myocardial infarction (MI)

(e) Angina pectoris

(f) Ventricular arrhythmias requiring continuous therapy

(g) Supraventricular arrhythmias including atrial fibrillation, which are uncontrolled.

(h) Haemorrhagic or thrombotic stroke, including transient ischaemic attacks or any other central nervous system bleeding

L-6 Patients with COPD or asthma.

L-8 Creatinine clearance < 50 mL/min calculated by Cockcroft-Gault equation.

L-9 Confirmed proteinuria > 1+ on dipstick testing.

Other exclusions

L-7 Current refractory nausea and vomiting, malabsorption syndrome, disease significantly affecting gastrointestinal function, resection of the stomach or small bowel, symptomatic inflammatory bowel disease or ulcerative colitis, or partial or complete bowel obstruction.

For procedures for withdrawal of incorrectly enrolled patients see Section 7.3 of the core protocol.

5.3 Lifestyle restrictions

Please refer to section 5.3 Lifestyle restrictions in the core protocol for guidance on contraception.

5.3.1 Restrictions applicable to durvalumab

Patients should not donate blood or blood components while participating in this study and through 90 days after receipt of the final dose of durvalumab or until alternate anticancer therapy is started.

Immunosuppressive medications including, but not limited to systemic corticosteroids at doses beyond 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumour necrosis factor alpha blockers are prohibited. Use of immunosuppressive medications for the management of study drug-related AEs and in patients with contrast allergies is acceptable. In addition, use of topical, inhaled and intranasal corticosteroids is permitted (see Table 3).

Live attenuated vaccines within 30 days of durvalumab dosing (ie, 30 days prior to the first dose, during treatment with durvalumab and for 180 days post-discontinuation of durvalumab). Inactivated viruses, such as those in the influenza vaccine, are permitted (see Table 3).

5.3.2 Restrictions applicable to vistusertib

Please refer to section 5.3 of the core protocol for contraception requirements.

5.3.2.1 Meals and dietary restrictions

- Vistusertib can be given with or without food.
- Sugary and fatty foods should be kept to a minimum in the meals prior to taking a dose.
- Large amounts of grapefruit and Seville oranges (and other products containing these fruits eg, grapefruit juice or marmalade) should be avoided whilst taking vistusertib.
- No more than a small glass of grapefruit juice (120 mL) or half a grapefruit or 1 to 2 teaspoons (15 g) of Seville orange marmalade daily is allowed.

5.3.2.2 Activity

Patients should be advised of the need for sunlight protection measures such as use of sunscreen during administration of vistusertib, and should be advised to adopt such measures for a period of 3 months after receiving their final dose of vistusertib.

5.3.2.3 Mucositis prevention measures

Patients should be educated on the common signs and symptoms of stomatitis and advised to report these promptly to their study physician should these occur. Patients should also be advised to:

- Perform consistent, regular, and thorough brushing with a soft toothbrush; floss after each meal
- Frequently rinse with bland rinses such as sterile water, normal saline, or sodium bicarbonate
- Avoid alcohol-containing rinses and toothpastes with sodium lauryl sulphate
- Avoid alcohol- or peroxidase-containing mouthwash products
- Avoid acidic, spicy, hard, or crunchy foods that may injure the oral epithelium, and consume foods that are tepid rather than hot
- Attend regular dental check-ups.

5.4 Screen failures

Please refer to Section 5.4 of the core protocol.

6. STUDY TREATMENTS

Study treatment is defined as any study drug(s) (including marketed product comparator and placebo) or medical device(s) intended to be administered to a study participant according to the study protocol. Study treatment in this Module 4 refers to durvalumab and vistusertib.

6.1 Treatments administered

6.1.1 Study drugs

Table 2 Study drugs

	Vistusertib	Durvalumab
Dosage formulation:	Supplied as 10, 25, 35, 50 and 62.5 mg tablets. Vistusertib tablets contain vistusertib, mannitol, microcrystalline cellulose, croscarmellose sodium, povidone and magnesium stearate. The tablet film coat comprises polyvinyl alcohol, titanium dioxide, polyethylene glycol 3350, talc and yellow iron oxide.	Supplied as a vialed liquid solution containing 500 mg (nominal) durvalumab per vial. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine hydrochloride, 275 mM trehalose dihydrate, 0.02% (weight/volume [w/v]) polysorbate 80, at pH 6.0. The nominal fill volume is 10.0 mL.
Route of administration:	Oral	IV infusion
Dosing instructions:	Vistusertib 125 mg BD. The tablets are to be administered orally on an intermittent schedule (2 days on, 5 days off).	Durvalumab 1500 mg via IV infusion Q4W ±2 days (fixed dosing for patients >30 kg bodyweight).
Packaging and labelling	Study treatment will be provided in bottles. Labels will be prepared in accordance with GMP and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labeling. Label text will be translated into local language, as required. Vistusertib will be provided with either single-panel labels or multi-language booklet labels. Specific dosing instructions will not be included on the label; the site must complete the "Patient Dispensing Card" with the details of the dosing instructions at the time of dispensing. The investigator's emergency contact details will not be on the label, but can be found in the informed consent and the 'Patient Dispensing Card'. For emergency purposes the patient must be in possession of the emergency contact details at all times.	Study drug will be provided in vials. Each vial will be labelled in accordance with GMP Annex 13 and per country regulatory requirement. Labels will be prepared in accordance with GMP and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language, as required. Durvalumab will be provided with either single-panel labels or multi-language booklet labels. The investigator's emergency contact details will not be on the label, but can be found in the informed consent and the 'Patient Emergency Card'. For emergency purposes, the patient must be in possession of the emergency contact details at all times.
Provider	AstraZeneca	AstraZeneca. Commercially available 0.9% (w/v) saline or 5% (w/v) dextrose IV bags will be supplied by each site.

BD twice daily; GMP Good Manufacturing Practice; IV=intravenous(ly); Q4W every 4 weeks; w/v weight/volume.

6.2 Preparation/handling/storage/accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study drugs received and any discrepancies are reported and resolved before use of the study treatment.

Only patients enrolled in the study may receive study treatment and only authorised site staff may supply or administer study drugs. All study drugs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study drug accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study drug are provided in the relevant appendices in the core protocol.

6.2.1 Durvalumab preparation and handling

Durvalumab will be supplied by AstraZeneca as a 500 mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine hydrochloride, 275 mM trehalose dihydrate, and 0.02% (weight/volume [w/v]) polysorbate 80; it has a pH of 6.0 and a density of 1.054 g/mL. The nominal fill volume is 10.0 mL.

Study drug vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. The vials should be kept in the original packaging until use to prevent prolonged light exposure.

The dose of durvalumab for administration must be prepared by the investigator's or site's designated study drug manager using aseptic technique. Total time from needle puncture of the durvalumab vial to the start of administration should not exceed 4 hours at room temperature or 24 hours at 2°C to 8°C (36°F to 46°F). Infusion solution must be allowed to equilibrate to room temperature prior to commencement of administration.

A dose of 1500 mg (for patients >30 kg body weight) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab concentration ranging from 1 to 15 mg/mL and delivered through an IV-administration set with a 0.2-µm or 0.22-µm filter. Add 30.0 mL (ie, 1500 mg) of durvalumab to an appropriately sized IV bag such that the final concentration is within 1 to 15 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

If a patient's body weight falls ≤30 kg during the study, (s)he will be withdrawn from the study treatment unless (s)he derives some clinical benefit according to the treating physician. In this case, and following agreement between the treating physician and the Sponsor, the

patient may continue treatment at a body-weight adapted dose of 20 mg/kg actual body weight.

Weight-based dosing at 20 mg/kg (for patients ≤30 kg) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab concentration ranging from 1 to 15 mg/mL, and delivered through an IV administration set with a 0.2-µm or 0.22-µm filter. An example of a weight-based dose calculation is shown in Section 6.2.1.1.

Standard infusion time is one hour (± 5 minutes), however if there are interruptions during infusion, the total allowed infusion time should not exceed 8 hours at room temperature.

If either preparation time or infusion time exceeds the time limits a new dose must be prepared from new vials. Durvalumab does not contain preservatives, and any unused portion must be discarded.

Do not co-administer other drugs through the same infusion line.

The IV line will be flushed with a volume of IV diluent equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered.

Durvalumab should be given at least 1 hour after the patient has taken their vistusertib morning dose (on vistusertib dosing days). Patients will be monitored before, during, and after the first durvalumab infusion with assessment of vital signs at the times specified in the SoA (Table 1) and Section 8.2.3 of the core protocol. If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be at the investigator's discretion (suggested 30 minutes after each durvalumab infusion). For management of patients who experience an infusion reaction, please refer to the toxicity and management guidelines for infusion-related reactions at the following location: https://tmg.azirae.com.

Durvalumab (1500 mg) will be administered via IV infusion Q4W ±2 days. Treatment with durvalumab will commence on Day 1 following confirmation of eligibility and will continue on a Q4W schedule until disease progression is confirmed.

6.2.1.1 Durvalumab weight-based calculation

If a patient's body weight falls ≤30 kg during the study, (s)he will be withdrawn from the study treatment unless (s)he derives some clinical benefit according to the treating physician. In this case, and following agreement between the treating physician and the Sponsor, the patient may continue treatment at a body-weight adapted dose of 20 mg/kg of durvalumab Q4W until the weight improves to >30 kg, at which point the patient should start receiving the fixed dosing of durvalumab 1500 mg Q4W:

3 Cohort dose: X mg/kg

4 Patient weight: Y kg

5 Dose for patient: XY mg = X (mg/kg) × Y (kg)

6 Dose to be added into infusion bag:

Dose (mL) = XY mg/50 (mg/mL) where 50 mg/mL is durvalumab nominal concentration. The corresponding volume of durvalumab should be rounded to the nearest tenth mL (0.1 mL). Dose adjustments for each cycle are only needed for greater than 10% change in weight.

7 The number of vials required for dose preparation is the next greatest whole number of vials from the following formula:
Number of vials = Dose (mL) / 10.0 (mL/vial)

Example:

8 Cohort dose: 20 mg/kg

(a) Patient weight: 30 kg

(b) Dose for patient: 600 mg = 20 (mg/kg) × 30 (kg)

(c) Dose to be added into infusion bag:

(d) Dose (mL) = 600 mg / 50 (mg/mL) = 12.0 mL

(e) The number of vials required for dose preparation:
Number of vials = 12.0 (mL) / 10.0 (mL/vial) = 2 vials

6.2.2 Vistusertib preparation and handling

Patients in Cohort A.4.RIC will be treated with vistusertib 125 mg BD orally on an intermittent schedule (2 days on, 5 days off), in combination with durvalumab at a dose of 1500 mg every 4 weeks via a 60-minute intravenous administration. For dose modification guidance, please see Section 8.4.5.1, Table 7.

Where possible all doses of vistusertib should be taken at approximately the same times each day. Twice daily doses should be taken approximately 12 hours apart. If vomiting occurs within 30 minutes after vistusertib dosing, or later if the tablet(s) can be identified in the vomit content, the patient can re-take a new tablet(s).

Should a patient miss a scheduled dose, the patient will be allowed to take the dose up to a maximum of 2 hours after the scheduled dose time. If greater than 2 hours after the scheduled dose time, the missed dose should not be taken and the patient should take their allotted dose at the next scheduled time. If a patient needs to take the dose earlier for whatever reason, the patient can take the dose up to 2 hours earlier than the scheduled dose time. The patient should make every reasonable effort to take the vistusertib tablet(s) on time.

6.2.3 Study drug administration

It is important to follow the assessment schedule as closely as possible.

Patients should continue to receive study treatment (ie, durvalumab in combination with vistusertib) until objective radiological disease progression as per Response Evaluation Criteria in Solid Tumours (RECIST 1.1), as long as, in the investigator's opinion, they are benefiting from treatment and they do not meet any other discontinuation criteria. Disease progression should be confirmed by a subsequent scan (no earlier than 4 weeks later) in the absence of clinically significant deterioration as assessed by the investigator. All patients who have objective progression of disease will enter follow-up.

6.2.4 Storage

All study drugs should be kept in a secure place under appropriate storage conditions.

Vistusertib tablets should be stored in the clinical pack at room temperature (below 30°C). For further information, investigators should refer to the study drug label.

Durvalumab is to be stored at the study centre in a secured facility with limited access and controlled temperature (2ºC to 8ºC). The temperature should be monitored on a daily basis and documented in the temperature monitoring log according to the study drug handling instructions.

The study drug must be kept in the original outer container and under conditions specified on the labels.

In the following cases, the centre staff should not use affected study drug and should immediately contact AstraZeneca representative for further guidance:

- Temperature excursion upon receipt or during storage at the study
- Damaged kit upon receipt
- Damaged vial/bottle

Damaged study drug should be documented according to the instructions provided by AstraZeneca representative. Storage conditions stated in the Investigator's Brochure, or the study drug Handling Instructions document, may be superseded by the label storage.

6.2.5 Accountability

The study drugs provided for this study should only be used as directed in the study protocol.

The study site staff will account for all study drugs received at the centre, for unused study drugs, and for appropriate destruction (according to local procedures). Certificates of delivery, destruction, and/or return should be signed.

The administration of all medications (including study drug) and details of treatment with study drug should be recorded in the appropriate sections of the electronic Case Report Form (eCRF).

Durvalumab will be administered IV at the study centre on treatment visits and within visit windows. Patients will self-administer vistusertib.

6.3 Measures to minimise bias: randomisation and blinding

This is an open-label study.

Recruitment to the biomarker-matched cohorts will be based upon a predefined schema (described in the Pathology and Genomic Testing Manual) for patient allocation which takes account of biomarker prevalence estimates and the platform of evidence for each study treatment.

If a patient withdraws from participation in the study, then his/her enrolment code cannot be reused. Withdrawn patients will not be replaced.

6.4 Treatment compliance

The administration of all study drugs (including study drug) should be recorded in the appropriate sections of the eCRF. Durvalumab will be administered on site. Treatment compliance will be assured by reconciliation of site drug accountability logs.

Patients should be given clear instructions on how and when to take their study treatment. Patients will self-administer vistusertib. Study site staff will make tablet counts at regular intervals during treatment. Compliance will be assessed by the tablet count and the information will be recorded in the appropriate section of the eCRF. After the tablet count has been performed, the remaining tablets will not be returned to the patient but will be retained by the investigative site until reconciliation is completed by the study physician. All patients must return their bottle(s) of vistusertib at the appropriate scheduled visit, when a new bottle will be dispensed. Patients will be instructed to notify study site personnel of missed doses. Dates of missed or held doses will be recorded by the patient on their patient diary and by the site staff on the eCRF.

Patients must return all containers and any remaining tablets at the end of the study.

Any change from the dosing schedule, dose interruptions, dose reductions, dose discontinuations should be recorded in the eCRF. Note: Dose reductions are not allowed for durvalumab without prior agreement with the study physician (see section 6.6).

The Study Drug Storage Manager is responsible for managing the study drug from receipt by the study site until the destruction or return of all unused study drug. The investigator(s) is/are responsible for ensuring that the patient has returned all unused study drug.

Use of study treatment in doses in excess of that specified in the protocol is considered to be an overdose. Refer to Section 8.4.3 for procedures in case of overdose.

6.5 Concomitant therapy

Any medication or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the patient received in the 4 weeks prior to starting study treatment, is receiving at the time of enrolment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

If medically feasible, patients taking regular medication other than those excluded from this study should be maintained on it throughout the study period.

Prohibited concomitant medications are described in Table 3. Please refer to Section 8.4.5 for guidance on management of study drug-related toxicities.

The use of concomitant medications must be recorded in the eCRF.

Table 3 Prohibited medications

Prohibited medication/class of drug:	
Unless stated otherwise, these medications are prohibited from the time that patients enter the main screening period until the last dose of study treatment. The pre-screen may be done whilst on prior therapy.	
Any investigational anticancer therapy other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment
Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment. (Note: concurrent use of hormones for non-cancer-related conditions [eg, insulin for diabetes and hormone replacement therapy] is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable [eg, by local surgery or radiotherapy]). Patients may receive treatment with bisphosphonates or RANKL inhibitors for the treatment of bone metastases

Table 3 Prohibited medications

Prohibited medication/class of drug:	
Immunosuppressive medications, including, but not limited to: systemic corticosteroids at doses exceeding 10 mg/day of prednisone or its equivalent, methotrexate, azathioprine, and tumour necrosis factor-α blockers	Should not be given concomitantly, or used for premedication prior to the infusions. The following are allowed exceptions: • Use of immunosuppressive medications for the management of study drug-related AEs • Short-term premedication for patients receiving combinations where the prescribing information for the agent requires the use of steroids for documented hypersensitivity reactions • Use in patients with contrast allergies • In addition, use of inhaled, topical, and intranasal corticosteroids is permitted. A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of non-immunotherapy related events experienced by the patient (eg, chronic obstructive pulmonary disease, radiation, nausea, etc).
Live attenuated vaccines	Prohibited from the time that patients enter the main screening period until 180 days after the last dose of study treatment.
Epidermal growth factor receptor (EGFR) Tyrosine kinase inhibitors (TKIs)	Should not be given concomitantly. Should be used with caution in the 90 days post last dose of durvalumab.
Herbal and natural remedies which may have immune-modulating effects	Should not be given concomitantly unless agreed by the sponsor

AE adverse event

The use of herbal preparations/medications should be discouraged throughout the study. These herbal medications include, but are not limited to: St. John's Wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone, yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 7 days prior to first dose of study drug (3 weeks for St John's Wort). Use of these products, as well as use of all vitamins, nutritional supplements and all prescribed concomitant medications, must be recorded in the eCRF.

Other concomitant treatment

Patients who begin Coumadin therapy should be advised to have their anticoagulation monitored more frequently when receiving vistusertib and should stop medication with vistusertib at thrombocytopenia Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or higher.

Patients may continue to receive therapeutic bisphosphonates or denosumab and erythropoietin preparations (Procrit®, Epogen®, Aranesp®), if they were receiving them prior to beginning study treatment.

Blood transfusions are allowed during the study.

Medication other than that described above, which is considered necessary for the patient's safety and wellbeing, may be given at the discretion of the investigator and recorded in the appropriate sections of the eCRF.

6.5.1 Rescue and supportive medication

The study site will supply rescue medication and this will be procured locally. The sponsor will supply only if required by local regulations.

The use of rescue medications is allowable at any time during the study. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

Supportive medication, described in Table 4, may be given at the discretion of the investigator and recorded in the appropriate sections of the eCRF.

Table 4 Supportive medication

Supportive medication/class of drug:	Usage:
Concomitant medications or treatments (eg, acetaminophen or diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care, except for those medications identified as "prohibited," as listed above	To be administered as prescribed by the investigator
Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy to non-target lesions, etc])	Should be used, when necessary, for all patients
Inactivated viruses, such as those in the influenza vaccine	Permitted

6.5.2 Effect of vistusertib on other drugs

Whilst patients may not enter a study arm if they have taken any of the CYP450 isoenzyme inhibitors or inducers (detailed in Sections 5.2 and 6.5) within the stated washout periods prior to study start, it could be possible to allow their short-term administration during the study under the following circumstances:

- If a patient requires short-term administration of a restricted CYP3A4/5, P-gp or BCRP inhibitor vistusertib treatment must be withheld for three days prior to administration and not restarted until the concomitant therapy has been discontinued for the appropriate time period described in Table 5.

- If a patient requires short-term administration of a restricted CYP3A4/5, P-gp (MDR1) or BCRP isoenzyme inducer this should be clearly documented in the eCRF and may then be permitted, but the investigator will be informed that this could lead to lower levels of study drug and a potential reduction in clinical efficacy.
- If a patient requires short term administration of restricted substrates of OATP1B1, OATP1B3, MATE1 or MATE2K vistusertib treatment must be withheld for 3 days prior to the first administration and not restarted until the concomitant therapy has been discontinued for the appropriate time period described in Table 6.

Information on any treatment in the 4 weeks prior to starting study treatment and all concomitant treatments given during the study with reasons for the treatment should be recorded. If medically feasible, patients taking regular medication other than those excluded from this study should be maintained on it throughout the study period.

The lists of CYP inhibitors, inducers and substrates are not exhaustive and the absence of a drug from these lists does not imply that its combination with vistusertib is safe.

Table 5 Cytochrome P450 CYP and transporter inhibitor/inducer restrictions

CYP enzymes	Inhibitors/inducers	Minimum washout period
CYP3A4/5 Strong competitive inhibitors	grapefruit juice, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin and voriconazole	1 week
CYP3A4/5 Strong time dependent inhibitors	boceprevir, clarithromycin, cobicistat, danoprevir, elvitegravir, LCL161, lopinavir, mibefradil*, posaconazole, ritonavir, telaprevir and tipranivir	2 weeks
CYP3A4/5 Strong inhibitors (classification unknown)	conivaptan	1 week
CYP3A4/5 Moderate competitive inhibitors	amprenavir, aprepitant, atazanavir, cimetidine, cyclosporine, fluconazole, imatinib and netupitant	1 week
CYP3A4/5 Moderate time dependent inhibitors	ACT-178882, casopitant, crizotinib, darunavir, diltiazem, erythromycin, ledipasvir, lomitapide, tofisopam and verapamil	2 weeks
	FK1706	half-life not found
CYP3A4/5 Moderate inhibitors (classification not known)	ciprofloxacin and dronedarone	1 week
	Schisandra sphenanthera	half-life not found

Table 5 Cytochrome P450 CYP and transporter inhibitor/inducer restrictions

CYP enzymes	Inhibitors/inducers	Minimum washout period
CYP3A4/5 Strong inducers	carbamazepine, phenytoin, rifabutin, rifampicin and St. John's Wort	3 weeks
	enzalutamide and phenobarbital	5 weeks
	mitotane	114 weeks
	avasimibe	half-life not found
CYP3A4/5 Moderate inducers	bosentan, genistein, lersivirine, lopinavir, modafinil, nafcillin, ritonavir, semagacestat, thioridazine and tipranavir	1 week
	etravirine	2 weeks
	efavirenz	3 weeks
	talviraline	half-life not found
P-gp (MDR1) inhibitors	dronedarone, erythromycin, indinavir, itraconazole, ketoconazole, lapatinib, lopinavir, ritonavir, quinidine and verapamil vorapaxer	1 week 10 weeks
	valspodar (PSC 833)	half-life not found
P-gp (MDR1) inducers	carbamazepine and rifampin	3 weeks
BCRP inhibitors	atazanavir, cyclosporine, lopinavir, ritonavir and tipranavir	1 week

CYP cytochrome; MDR1 multidrug resistance protein 1; P-gp P-glycoprotein.

Table 6 Transport substrate restrictions

Transporters	Substrates
OATP (1B1&1B3)	bosentan, fexofenadine, glyburide, pitavastatin, pravastatin, **repaglinide**, rosuvastatin
MATE (1 & 2K)	cisplatin

MATE multidrug and toxin extrusion protein; OATP organic anion transporting protein
Substrates in bold type have a narrow therapeutic index. Reference Araki K et al 2009; Beziaud L et al 2009; Bloomer et al 2013). Washout periods should be 5 x reported terminal half-lives.

6.6 Dose modification and discontinuation

For patients who weigh >30 kg, the dose of durvalumab cannot be modified. If a patient's body weight falls ≤30 kg during the study, (s)he will be withdrawn from the study treatment unless (s)he derives some clinical benefit according to the treating physician. In this case, and

following agreement between the treating physician and the Sponsor, the patient may continue treatment at a body-weight adapted dose of 20 mg/kg actual body weight.

Durvalumab dosing can be interrupted in the event of treatment-related toxicity. All toxicities will be graded according to Common Toxicity Criteria for Adverse Events (CTCAE) version 4.03. Dose reductions are not permitted without prior agreement with the study physician. Please refer to the toxicity management guidelines for durvalumab at the following location: URL: https://tmg.azirae.com.

Dose reductions or interruptions of vistusertib, and initiation of supportive care, are allowed as deemed appropriate by the treating physician. If Day 1 treatment with durvalumab is interrupted, then both study medications will be delayed until the combination can be resumed. Dose reduction and discontinuation guidelines for haematological and non-haematologic toxicities for vistusertib are shown in Section 8.4.5.2 and dose modification guidance can be discussed with the study physician if investigators wish to deviate from the guidance based on their medical assessment. A continuous dosing schedule may be recommended.

If the toxicity resolves or reverts to CTCAE Grade ≤2 within 2 treatment weeks and the patient is showing clinical benefit per the investigator, study treatment with vistusertib may be restarted.

In order to initiate a new cycle of therapy with durvalumab and vistusertib, the patient must have an absolute neutrophil count (ANC) ≥1,000/µL and a platelet count ≥50,000/µL and no drug-related non-haematological Grade ≥3 toxicity on Day 1.

If these criteria are not met (but the patient derives clinical benefit), the entire cycle with all drugs is to be delayed to a maximum of 4 treatment weeks (33 days [4 weeks ie, 28 days + 5 from the drug holiday in previous week, which still counts as a “treatment week”] for vistusertib). Treatment may only be restarted once the results of repeat assessments indicate that these criteria have been met.

If either durvalumab or vistusertib treatment is discontinued for more than 33 days, the patient should permanently discontinue study treatment. However, for patients allocated to this biomarker matched cohort (A.4.RIC) who, in the opinion of the investigator would benefit from continued treatment with vistusertib whilst durvalumab is discontinued, may continue treatment with prior approval from the Study Physician.

6.7 Treatment after the end of the study

Patients are permitted to either receive standard of care therapy, or to continue to receive study treatment following the end of the study if, in the opinion of the investigator, they are continuing to receive benefit from treatment. After discontinuation of study treatment, the

investigator will be at liberty to define further most appropriate anti-cancer treatment. Subsequent anti-cancer treatment is expected to be initiated following the cancer recurrence or development of a new cancer. Information on subsequent anti-cancer therapies should be recorded on the clinical database.

7. DISCONTINUATION OF TREATMENT AND PATIENT WITHDRAWAL

Please refer to Section 7 in the core protocol. Guidance on re-allocation to a second treatment cohort is provided in Section 7.4 of the core protocol.

Due to the discontinuation of the vistusertib programme, no patients will be re-allocated to Module 4.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in the SoA (Table 1).

8.1 Efficacy assessments

Please refer to the core protocol.

8.2 Safety assessments

8.2.1 Clinical safety laboratory assessments

Please refer to core protocol.

8.2.1.1 Coagulation

Please refer to core protocol.

8.2.1.2 Other safety assessments

Please refer to core protocol.

8.2.1.3 Pneumonitis (interstitial lung disease) investigation

The following assessments, and additional assessments if required, will be performed to enhance the investigation and diagnosis of potential cases of pneumonitis. The results of the assessment will be collected.

- Physical examination; Signs and symptoms (cough, shortness of breath and pyrexia, etc) including auscultation for lung field will be assessed.
- SpO_2; Saturation of peripheral oxygen (SpO_2)
- Other items; When pneumonitis (interstitial lung disease [ILD]) is suspected during study treatment, the following markers should be measured where possible:
  - ILD Markers (KL-6, SP-D) and β-D-glucan

– Tumour markers: Particular tumour markers which are related to disease progression.

8.2.2 Physical examinations

Please refer to core protocol.

8.2.3 Vital signs

Please refer to core protocol.

8.2.4 Electrocardiograms

Please refer to core protocol

8.2.5 Performance status

Please refer to core protocol

8.3 Collection of adverse events

Please refer to the core protocol.

8.4 Safety reporting and medical management

8.4.1 Reporting of serious adverse events

Please refer to the core protocol.

8.4.2 Pregnancy

Please refer to the core protocol.

8.4.3 Overdose

A dose of vistusertib in excess of that specified according to the protocol will constitute an overdose. There is currently no known antidote to vistusertib, and the treatment of overdose should be supportive for the underlying symptoms. To date, no patient receiving vistusertib has experienced an overdose associated with AEs.

8.4.4 Medication error

Please refer to the core protocol.

8.4.5 Management of study-drug related toxicities

At this time, there are limited safety data regarding the combination of durvalumab and vistusertib. Given the differing mechanisms of action of durvalumab and vistusertib, the potential for potentiation of toxicities is thought to be limited. Some toxicities, for example pneumonitis and asthenia/fatigue may, on theoretical grounds, be potentiated in the combination arm and particular attention should be paid to these.

In the event of toxicity in this combination arm of the study which cannot be managed by supportive measures alone, stopping one or both medications should be an investigator decision based on the available information and, if necessary, following discussion with the sponsor.

The following general guidance should be followed for management of toxicities:

- Treat each of the toxicities with maximum supportive care (including withholding the agent suspected of causing the toxicity if required).
- If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of the assigned study drug along with appropriate continuing supportive care. If medically appropriate, dose modifications are permitted for vistusertib. In addition, guidelines on vistusertib dose modifications are provided in Section 8.4.5.2. In the event of toxicity that cannot be managed by following the toxicity management guidelines for vistusertib and durvalumab, consider stopping treatment with vistusertib.

All dose modifications should be documented with clear reasoning and documentation of the approach taken. Dose reductions are not permitted without prior agreement with the study physician.

8.4.5.1 Management of durvalumab-related toxicities

Please refer to the toxicity management guidelines for durvalumab at the following location: URL: https://tmg.azirae.com.

8.4.5.2 Management of vistusertib-related toxicities

Patients receiving the combination of durvalumab plus vistusertib may report AEs that are known to be associated with vistusertib alone. Management guidelines for such AEs (eg, hyperglycaemia, haematological toxicities) are provided below.

Adverse events of special interest for vistusertib

AEs of interest are events are of scientific and medical interest specific to the further understanding of the vistusertib safety profile and require close monitoring and rapid communication by the investigator to the sponsor. Vistusertib AEs of interest may be serious or non-serious. The rapid reporting of these AEs of interest allows ongoing analysis of these events in order to characterise and understand them in association with the use of this study drug. Further information on vistusertib AEs of interest is provided in the Investigator's Brochure.

Management of vistusertib-related toxicities in general

If a patient has a clinically significant and/or unacceptable toxicity, not attributable to the disease or disease-related processes under investigation, where the investigator considers the

AE of concern to be specifically associated with vistusertib, dosing will be interrupted and/or the dose reduced and supportive therapy administered as required.

In order to initiate a new cycle of therapy with durvalumab and vistusertib, the patient must have an ANC ≥1,000/μL and a platelet count ≥50,000/μL and no drug-related non-haematological Grade ≥3 toxicity on Day 1.

If these criteria are not met (but the patient derives clinical benefit), the entire cycle with all drugs is to be delayed to a maximum of 4 treatment weeks (33 days [4 weeks ie, 28 days + 5 from the drug holiday in previous week, which still counts as a "treatment week"] for vistusertib). Treatment may only be restarted once the results of repeat assessments indicate that these criteria have been met.

Substantial acute toxicities should be managed as medically indicated and with temporary suspension of study drug, as appropriate.

Dose reductions or holds and initiation of supportive care are allowed as clinically indicated by the study physician. In general, for each patient, a maximum of 2 dose reductions of vistusertib will be allowed, however, exceptions form this rule may be discussed with the AstraZeneca study physician on a case-by-case basis. The vistusertib dose level modification is presented in Table 7.

Table 7 Recommended dose reductions for vistusertib for management of treatment-emergent toxicities

Dose level	Vistusertib monotherapy dose (2 days on, 5 days off)
Starting Dose vistusertib	125 mg BD
-1 Dose Level	100 mg BD
-2 Dose Level	75 mg BD
-3 Dose Level	50 mg BD in discussion with AstraZeneca study physician

BD twice daily
NB : The dose of durvalumab is 1500 mg, given by a 60-minute infusion every 4 weeks. There are no dose reductions for durvalumab in this study.

In general, if a patient experiences a Grade 1/Grade 2 haematological or non-haematological toxicity, no dose modification of vistusertib is required.

If a patient experiences a Grade 3 or Grade 4 toxicity, not attributable to the disease or disease-related processes under investigation, dosing will be interrupted and/or the dose reduced) see (Table 7) and supportive therapy administered as required.

If the toxicity resolves or reverts to CTCAE Grade ≤2 within 2 treatment weeks and the patient is showing clinical benefit, treatment with vistusertib may be restarted.

If the toxicity does not resolve to CTCAE Grade ≤2 after 2 weeks of treatment and the patient does not show clinical benefit, then the patient should be withdrawn from the study and observed until resolution of the toxicity. For an intermittent dosing break, the maximum number of days allowed is 19 days (14 days + 5 from the drug holiday in Week 1, which still counts as "treatment week").

If the toxicity does not resolve to CTCAE Grade ≤2 after 2 weeks of treatment but the patient does show clinical benefit, treatment with vistusertib may be restarted after discussion with the study physician.

The investigator may make dose modifications if he considers these are related to the combination therapy, please refer to Section 8.4.5.3.

Management of vistusertib-associated haematological toxicities

Durvalumab is not known to be associated with haematological toxicities. The following guidelines are specific to vistusertib, as such AEs are known to be associated with this agent. The investigator should consider referral to a haematology specialist when patients in the module report any of the haematological events outlined in Table 8.

Dose modification guidance can be discussed with the study physician if investigators wish to deviate from the guidance based on their medical assessment.

Generally, Grade 1 or 2 haematological toxicities do not require vistusertib dose reductions and should be managed as medically indicated (with or without short dose interruptions) by the study physician.

If the CTCAE Grade 3 toxicity resolves or reverts to CTCAE Grade ≤2 within 2 treatment weeks and the patient is showing clinical benefit per the investigator, study treatment with vistusertib may be restarted.

For all CTCAE Grade 4 toxicities, except haematological toxicities, permanently discontinue vistusertib. Refer to table 9 for management of CTCAE Grade 3/4 haematological toxicities.

For vistusertib in monotherapy or in combination with agents which do not affect the bone marrow, no specific monitoring measures must be put in place beside standard monitoring in clinical trials, including regular blood checks as per protocol and if findings should be reported, blood checks should be amended accordingly.

In general, treatment with prophylactic haematopoietic growth factors is not allowed and should only be permitted during drug holidays as per FDA guidance (Smith et al 2006).

Table 8 Dose modifications and discontinuation criteria for CTCAE Grade 3/4 haematological toxicities

Toxicity Grade	Vistusertib Action
Febrile neutropenia Grade 3 or 4	Immediately withhold **vistusertib** until infection is resolved, antibiotics no longer required and ANC Grade ≤2 or baseline **Vistusertib** restart with 1st dose reduction (see Table 7)
2nd episode of **febrile neutropenia** Grade 3 or 4	Immediately withhold **vistusertib** until infection is resolved, antibiotics no longer required and ANC Grade ≤2 or baseline **Vistusertib** restart with 2nd dose reduction (see Table 7)
3rd episode of **febrile neutropenia** Grade 3 or 4	Immediately discontinue **vistusertib**
Non-febrile neutropenia Grade 4 lasting >7 days despite growth factor support	Withhold **vistusertib** until Grade ≤2 or baseline **Vistusertib** restart with 1st dose reduction (see Table 7)
2nd episode of **non-febrile neutropenia** Grade 4 lasting >7 days despite growth factor support	Withhold **vistusertib** until Grade ≤2 or baseline **Vistusertib** restart with 2nd dose reduction (see Table 7)
3rd episode of **non-febrile neutropenia** Grade 4 lasting >7 days despite growth factor support	Withhold **vistusertib** until Grade ≤2 or baseline **Vistusertib** restart with 3rd dose reduction (see Table 7)
4th episode of **non-febrile neutropenia** Grade 4 lasting >7 days despite growth factor support	Discontinue **vistusertib**
Thrombocytopenia, Grade 4 without bleeding requiring red blood cell (RBC) transfusion	Withhold **vistusertib** until Grade ≤2 or baseline **Vistusertib** restart with 1st dose reduction (see Table 7)
2nd episode of **thrombocytopenia**, Grade 4 without bleeding requiring RBC transfusion	Withhold **vistusertib** until Grade ≤2 or baseline **Vistusertib** restart with 2nd dose reduction (see Table 7)
3rd episode of **thrombocytopenia**, Grade 4 without bleeding requiring RBC transfusion	Withhold **vistusertib** until Grade ≤2 or baseline **Vistusertib** restart with 3rd dose reduction (see Table 7)
4th episode of **thrombocytopenia**, Grade 4 without bleeding requiring RBC transfusion	Discontinue **vistusertib**
Thrombocytopenia, Grade 3 or 4 **with bleeding** requiring RBC transfusion	Withhold **vistusertib** until Grade ≤2 or baseline

Table 8 Dose modifications and discontinuation criteria for CTCAE Grade 3/4 haematological toxicities

Toxicity Grade	Vistusertib Action
	Vistusertib restart with 1st dose reduction (see Table 7).
2nd episode of **thrombocytopenia**, Grade 3 or 4 **with bleeding** requiring RBC transfusion	Withhold **vistusertib** until Grade ≤2 or baseline **Vistusertib** restart with 2nd dose reduction (see Table 7)
3rd episode of **thrombocytopenia**, Grade 3 or 4 **with bleeding** requiring RBC transfusion	Discontinue **vistusertib**

Management of non-haematological vistusertib-associated toxicities

Recommendations for the treatment of nausea and vomiting

Not all patients require antiemetics and therefore they should not be given prophylactically. However, once a patient has experienced nausea and vomiting, serotonin (5-HT3) antagonists should be administered on subsequent vistusertib dosing days, eg, dolasetron 100 mg by mouth daily, granisetron 2 mg by mouth daily or 1 mg by mouth BD. Please see National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: Antiemesis for further information (Moore et al 2016).

Aprepitant should not be used as it is a moderate CYP3A4/5 inhibitor.

Please refer to Table 7 for dose modifications required for Grade ≥3 nausea and/or vomiting.

If nausea and vomiting are not being managed with the regimen above, start a breakthrough treatment with the addition of one agent of a different drug class, eg:

- Dexamethasone 8 mg per os/oral (PO) at day 1 of the vistusertib dosing period or
- Metoclopramide 10 to 40 mg PO or
- Olanzapine 5 to 10 mg PO or
- Promethazine (Phenergan) 12.5 to 25 mg every 6 hours on the vistusertib dosing days prior to administering the vistusertib dose.

Should upper abdominal pain develop a H2 blocker or proton pump inhibitors can be added. For combinations, please refer to the manufacturers SMPC for the combination agent.

Recommendations for treatment of decreased appetite

Decreased appetite should be treated according to local clinical practice. Dietary review is recommended.

Recommendations for treatment of stomatitis/oral mucositis/mouth ulcers

For further information please refer to published guidelines (Pedicord et al 2015; Seiler et al 2014). For mild toxicity (Grade 1), use conservative measures such as non-alcoholic mouth wash or salt water (0.9%) mouth wash several times immediately after drug administration (1 to 3 hours) and during the day as required until resolution.

For more severe toxicity (Grade ≥2), the suggested treatment includes dexamethasone based mouthwashes with 10 ml of commercially available 0.5 mg/5 ml dexamethasone oral solution to swish x 2 min. In addition, topical analgesic mouth treatments (ie, local anaesthetics such as benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, or phenolic compounds) may be used. Importantly, patients must be instructed to swish and expectorate the mouth rinse to avoid systemic exposure to dexamethasone. Agents containing hydrogen peroxide, iodine, and thyme derivatives may worsen mouth ulcers. It is preferable to avoid these agents.

For Grade 3 stomatitis/oral mucositis/mouth ulcers, systemic pain killers are indicated (eg, oral or subcutaneous morphine) and dose modification as described in Table 7.

Recommendations for treatment of hyperglycaemia

In general, management of hyperglycaemia should be performed according to local standards at the discretion of the investigator.

Due to the predicted short half-life of vistusertib, only a short period of hyperglycaemia with insulin resistance might be expected. Therefore early treatment with insulin and/or oral anti-diabetes medication should be carefully evaluated and blood sugars and potassium levels monitored as per standard clinical practice. If blood glucose levels are <250 mg/dl (Grade 2), generally no medical treatment is required. Dietary modification may be initiated.

For Grade ≥3 hyperglycaemia, dose modifications are required (see Table 7).

Recommendations for evaluation and treatment of electrolyte changes including hypokalaemia and hypophosphataemia

Vistusertib, like other mTOR inhibitors inhibits pump mechanisms in renal tubules, leading to hypokalaemia and hypophosphataemia in a small proportion of patients. The presence of biochemical abnormalities should be monitored as per the protocol and electrolyte abnormalities should be corrected using oral supplements. The investigator should also

consider whether other medication the patient may be receiving, such as diuretics may have contributed to these abnormalities.

Reproductive organs

Reproductive toxicity has been classified as an important potential risk for vistusertib.

Any reports of pregnancy in patients, or partners of patients, will be followed up as described in the study protocol. Contraceptive measures during treatment with vistusertib are summarised in Section 8.4.2 of the core protocol.

Potential for phototoxicity

Phototoxicity has been classified as a potential risk for vistusertib; however, there have been no relevant clinical findings so far. Sunlight protection measures, including sunglasses should be adopted during treatment with vistusertib (See Section 5.3.2.2 of this document).

Recommendations for evaluation and treatment of renal effects

Renal effects have been classified as a potential risk for vistusertib. However, no clinically significant renal findings were reported at any dose of vistusertib so far.

Clinical study protocols exclude patients with impaired renal function or concurrent specific renal disease from participation in studies of vistusertib.

If Grade ≥2 renal dysfunction develops while the patient is on study, follow dose modification advice shown in Table 7.

Recommendations for evaluation and treatment of liver function test abnormalities

Evidence of abnormal liver function should be monitored as per the protocol guidelines. Increased levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), or serum bilirubin should trigger an investigation of the cause, which may include viral infection or disease progression with liver infiltration. The investigator should consider whether the abnormal liver function meets the criteria for expedited reporting; see core protocol (actions required in case of increases in liver biochemistry and evaluation of Hy's Law).

Vistusertib is metabolized in the liver. For patients who develop mild liver impairment while on study (Child-Pugh Class A), the recommended dose for vistusertib is 2 dose levels lower than the starting dose (see Table 7); if a dose 2 levels lower than the starting dose is not available, vistusertib should be discontinued. Patients who develop moderate or severe hepatic impairment (Child-Pugh Class B or C) must hold study drug until resolved to mild

impairment (Child-Pugh Class A) or better and will be re-treated at 2 dose levels lower than the starting dose for vistusertib (or discontinue if applicable) (see Table 7).

Recommendations for Evaluation and Treatment of Infections

Patients receiving treatment with vistusertib may be at an increased risk of infection. This should be managed as per clinical practice. In case of Grade 3 infections, the guidelines provided in the toxicity management guidelines for durvalumab at https://tmg.azirae.com should be followed.

8.4.5.3 Management of shared toxicities of vistusertib and durvalumab

The safety profiles of durvalumab and vistusertib have been subject to internal evaluation by AstraZeneca. The evaluation revealed that there is limited potential for potentiation of the known adverse drug reactions of both agents, due to the different pharmacological mechanisms of action. The 2 agents have some ADRs in common, eg, diarrhoea, rash (including rash of infusion-related reactions), pneumonitis, fatigue and hepatic toxicity, and there is a potential for an increased risk of these overlapping toxicities. Patients in this module will be closely monitored for these such treatment-emergent events.

In the event of toxicity in the combination arm of the study that cannot be managed by supportive measures alone, consider stopping or reducing the dose of vistusertib. The recommended dose reductions for vistusertib are presented in Table 7.

Toxicity management guidelines for combination therapy (durvalumab plus vistusertib)

Specific management guidelines for AEs that are associated with both vistusertib and durvalumab, such as diarrhoea, rash (including rash of infusion-related reactions), pneumonitis, fatigue and hepatic toxicity should be managed according to the guidelines provided.

The general guidance in Section 8.4.5 should be followed for management of toxicities:

In addition, the following are recommended:

- Patient evaluation to identify any alternative aetiology.
- In the absence of a clear alternative aetiology, all events of an inflammatory nature should be considered to be immune-related.
- Symptomatic and topical therapy should be considered for low-grade events.
- For persistent (greater than 3 to 5 days) low-grade (Grade 2), or severe (Grade ≥3) events promptly start prednisone PO 1 to 2 mg/kg/day or IV equivalent.
- If symptoms recur or worsen during corticosteroid tapering (≥4 weeks of taper), increase the corticosteroid dose (prednisone dose [eg, up to 2 to 4 mg/kg/day or IV equivalent])

until stabilisation or improvement of symptoms, then resume corticosteroid tapering at a slower rate.

- More potent immunosuppressives (refer to individual sections of the immune-related AE for specific type of immunosuppressive) should be considered for events not responding to systemic steroids.
- Discontinuation of study drug is not mandated for Grade 3/Grade 4 inflammatory reactions attributed to local tumour response (eg, inflammatory reaction at sites of metastatic disease, lymph nodes etc). Continuation of study drug in this situation should be based upon a benefit/risk analysis for that patient and be discussed with the study physician.
- If the CTCAE Grade 3 toxicity resolves or reverts to CTCAE Grade ≤2 within 4 treatment weeks and the patient is showing clinical benefit per the investigator, study treatment with vistusertib and durvalumab may be restarted.

For all CTCAE Grade 4 toxicities, permanently discontinue vistusertib and durvalumab.

8.5 Pharmacokinetics

Please refer to the core protocol.

8.6 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7 Genetics

Please refer to the core protocol.

8.8 Biomarkers

Please refer to the core protocol.

8.9 Medical Resource Utilisation and Health Economics

Medical Resource Utilisation and Health Economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

Please refer to the core protocol.

10. REFERENCES

Araki K et al 2009
Araki K, Turner AP, Shaffer VO, Gangappa S, Keller SA, Bachmann MF et al. mTOR regulates memory CD8 T-cell differentiation. Nature. 2009 Jul 2;460(7251):108-12.

Basu et al 2015
Basu B, Dean E, Puglisi M, Greystoke A, Ong M, Burke W et al. First-in-Human Pharmacokinetic and Pharmacodynamic Study of the Dual m-TORC 1/2 Inhibitor AZD2014. Clin Cancer Res. 2015;21(15):3412-9.

Beziaud L et al 2009
Beziaud L, Mansi L, Ravel P, Marie-Joseph EL, Laheurte C, Rangan L et al. Rapalogues Efficacy Relies on the Modulation of Antitumor T-cell Immunity. Cancer Res. 2016 Jul 15;76(14):4100-12

Bloomer et al 2013
Bloomer J, Derimanov G, Dumont E, Ellens H, Matheny C. Optimizing the in vitro and clinical assessment of drug interaction risk by understanding co-medications in patient populations. Expert Opin Drug Metab Toxicol. 2013 Jun;9(6):737–51.

Cheng et al 2015
Cheng H, Zou Y, Ross JS, Wang K, Liu X, Halmos B, RICTOR Amplification Defines a Novel Subset of Patients with Lung Cancer Who May Benefit from Treatment with mTORC1/2 Inhibitors. Cancer Discov. 2015 Dec;5(12):1262–70.

Garassino et al 2017
Garassino M, Vansteenkiste J, Joo-Hang Kim, Hervé Léna, Mazières J, Powderly J, Dennis P, Huang Y, Wadsworth C, Rizvi N. PL04a.03: Durvalumab in ≥3rd-Line Locally Advanced or Metastatic, EGFR/ALK Wild-Type NSCLC: Results from the Phase 2 ATLANTIC Study. J Thor Onc 2017;12:S10–S11.

Guichard et al 2015
Guichard SM, Curwen J, Bihani T, D'Cruz CM, Yates JW, Grondine M, et al. AZD2014, an Inhibitor of mTORC1 and mTORC2, Is Highly Effective in ER+ Breast Cancer When Administered Using Intermittent or Continuous Schedules. Mol Cancer Ther. 2015 Nov;14(11):2508-18.

Hirayama Y et al 2016
Hirayama Y, Gi M, Yamano S, Tachibana H, Okuno T, Tamada S et al. Anti-PD-L1 treatment enhances the antitumor effect of everolimus in a mouse model of renal cell carcinoma. Cancer Sci. 2016 Dec; 107(12): 1736–1744.

Jiang et al 2011
Jiang Q, Weiss JM, Back T, Chan T, Ortaldo JR, Guichard S, Wiltrout RH. mTOR kinase inhibitor AZD8055 enhances the immunotherapeutic activity of an agonist CD40 antibody in cancer treatment. Cancer Res. 2011 Jun 15;71(12):4074–84

Langdon et al, submitted publication
Combination of dual mTORC1/2 inhibition and αCTLA4 immune-checkpoint blockade potentiates anti-tumour immunity.

Lastwika et al 2016
Lastwika K, Wilson W, Li QJ, Norris J, Xu H, Ghazarian SR et al. Control of PD-L1 Expression by Oncogenic Activation of the AKT-mTOR Pathway in Non-Small Cell Lung Cancer. Cancer Res; 76(2); 227–38.

Mannick et al 2014
Mannick JB, Del Giudice G, Lattanzi M, Valiante NM, Praestgaard J, Huang B, et al. mTOR inhibition improves immune function in the elderly. Sci Transl Med. 2014 Dec 24;6(268):268

Moore EC et al 2016
Moore EC, Cash HA, Caruso AM, Uppaluri R, Hodge JW, Van Waes C and Allen CT. Enhanced Tumour Control with Combination mTOR and PD-L1 Inhibition in Syngeneic Oral Cavity Cancers. Cancer Immunol Res. 2016 Jul;4(7):611-20.

NCCN 2015
NCCN. 2015. NCCN Clinical Practice Guidelines in Oncology Antiemesis, Version 1. NCCN.

Narwal et al 2013
Narwal R, Roskos LK, Robbie GJ. Population Pharmacokinetics of Sifalimumab, an Investigational Anti-Interferonalpha Monoclonal Antibody, in Systemic Lupus Erythematosus. Clin Pharmacokinet 2013;52:1017–27.

Ng et al 2006
Ng CM, Lum BL, Gimenez V, Kelsey S, Allison D. Rationale for fixed dosing of pertuzumab in cancer patients based on population pharmacokinetic analysis. Pharm Res 2006;23(6):1275–84.

Pedicord VA et al 2015
Pedicord VA, Cross JR, Montalvo-Ortiz W, Miller ML, Allison JP. Friends Not Foes: CTLA-4 blockade and mTOR Inhibition Cooperate during CD8+ T Cell Priming To Promote Memory Formation and Metabolic Readiness. J Immunol. 2015 Mar 1;194(5):2089-98.

Seiler et al 2014
Seiler S, Koose J, Loibl S, & Jackisch C. 2014. "Adverse event management of oral mucositis in patients with breast cancer." Breast Care (Basel) 9:232–237.

Smith et al 2006
Smith TJ, Khatcheressian J, Lyman GH, et al. 2006. 2006 update of recommendations for the use of white blood cell growth factors: An evidence-based clinical practice guideline. J Clin Oncol 24:3187–205.

Tabernero et al 2008
Tabernero J, Rojo F, Calvo E, Burris H, Judson I, Hazell K et al. Dose- and schedule-dependent inhibition of the mammalian target of rapamycin pathway with everolimus: a phase I tumor pharmacodynamic study in patients with advanced solid tumors. J Clin Oncol 2008;1;26(10):1603-10.

Wang et al 2009
Wang DD, Zhang S, Zhao H, Men AY, Parivar K. Fixed dosing versus body size based dosing of monoclonal antibodies in adult clinical trials. J Clin Pharmacol 2009;49(9):1012–24.

Zhang et al 2012
Zhang S, Shi R, Li C, Parivar K, Wang DD. Fixed dosing versus body size-based dosing of therapeutic peptides and proteins in adults. J Clin Pharmacol 2012;52(1):18–28.

Zheng et al 2015
Zheng B, Mao JH, Qian L Zhu H, Gu D3, Pan XD et al. Pre-clinical evaluation of AZD-2014, a novel mTORC1/2 dual inhibitor against renal cell carcinoma. Cancer Letters 2015;357:468-475

Clinical Study Protocol

Drug Substance	Umbrella study
Study Code	D6185C00001 (HUDSON)
Version	14.0
Date	09 October 2024

Appendix M

Module 5: Durvalumab plus oleclumab

An Open-Label, Multi-Drug, Biomarker-Directed, Multi-Centre Phase II Umbrella Study in Patients with Non-Small Cell Lung Cancer, who Progressed on an Anti-PD-1/PD-L1 Containing Therapy (HUDSON)

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

Regulatory Agency Identification Numbers:

EudraCT number: 2017-002208-28

EU CT number: 2023-509004-15-00

IND number: 138050

VERSION HISTORY

Version 14.0, 09 October 2024
Key amendments and rationale for changes: The version number of this module has been revised in line with the other modules in the HUDSON study; however, no changes have been made to this module.

Version 13.0, 14 December 2023
Key amendments and rationale for changes: **Front page:** EU CT number has been added in line with the core CSP.

Version 12.0, 01 March 2023
Key amendments and rationale for changes: **Section 6.2, preparation/handling/storage/accountability:** Added a reference to the Pharmacy Manual.

Version 11.0, 16 August 2022
Key amendments and rationale for changes: The version number of this module has been revised in line with the other modules in the HUDSON study; however, no changes have been made to this module.

Version 10.0, 12 April 2022
Key amendments and rationale for changes: **Table 1, schedule of activities**: Addition of footnote to clarify the activities for patients continuing on study treatment after the data cut-off for the module clinical study report.

Figure 1, study design: Addition of footnote to clarify survival follow-up of screen failures and optional patient treatment re-allocation to a second treatment cohort are no longer required from implementation of protocol v10.0. Text for optional re-allocation to a second treatment cohort also included in text in Section 7, discontinuation of treatment and patient withdrawal.

Section 2.2, background: Reference to approval of durvalumab for the treatment of urothelial carcinoma in the US removed due to voluntary withdrawal of this indication in this country. Text also added to clarify the weight-based regimen (10 mg/kg every 2 weeks) is approved for urothelial carcinoma.

Section 2.2.1.2, durvalumab data: Number of patients treated with durvalumab updated to align with durvalumab IB Edition 17.

Section 7, discontinuation of treatment and patient withdrawal: Text added to clarify patient optional treatment re-allocation to a second treatment cohort is no longer required from implementation of protocol v10.0.

Section 8.6, pharmacodynamics: Text updated to clarify pharmacodynamic parameters will be evaluated in the study and a cross reference to Section 8.6 of the core protocol added.

Version 9.0, 14 May 2021

Key amendments and rationale for changes:

The version number of this module has been revised in line with the other modules in the HUDSON study; however, no changes have been made to this module.

Version 8.0, 11 September 2020

The version number of this module has been revised in line with the other modules in the HUDSON study; however, no changes have been made to this module.

Version 7.0, 21 May 2020

Key amendments and rationale for changes:

Section 2.2 Background: Updates to the registered use and approvals for durvalumab.

Section 4.1 Study design: Added statement that Cohort B.5.PRI closed recruitment early, as per core protocol Section 9.2, due to lack of positive efficacy data from the other 2 cohorts in the module which have completed enrolment.

Figure 2 (study flow diagram): this figure has been removed from all modules and a cross reference added to the same figure in the core protocol instead. Change made to limit the number of modules requiring updating during a protocol amendment whenever a new module is added.

Section 6.2.1 Durvalumab preparation and handling and **Section 6.2.2 Oleclumab preparation and handling:** Clarification that if the final product is stored at both refrigerated and ambient temperatures, the total time should not exceed 24 hours.

Section 6.4 Treatment compliance and **Section 6.6 Dose modification and discontinuation:** Clarification that dose reductions are not permitted.

Version 6.0, 05 November 2019

Key amendments and rationale for changes:

Table 1 Schedule of Activities: Footnote added that ad-hoc collection of survival status may be requested for OS analyses. Requirement for blood samples to be collected for oleclumab ADA testing removed due to the data providing limited information to the oleclumab programme and to reduce the blood sampling burden for patients.

Section 2.2 Background: Text updated to align with Edition 15 of the durvalumab IB and Edition 6 of the oleclumab IB.

Section 2.3.2 Potential risks of oleclumab in combination with durvalumab: Text updated to align with Edition 6 of the oleclumab IB.

Figure 2 Study flow diagram: Updated to reflect the addition of Modules 6 and 7.

Section 4.3.1 Justification of durvalumab dose: Correction of typographical errors and to align with Edition 15 of the durvalumab IB.

Section 5.2 Exclusion criteria: Module 5-specific exclusion criteria updated in light of emerging safety data.

Section 6.2.1 Durvalumab preparation and handling: Change to the window around the duration of durvalumab infusion to ±15 minutes. The previous window of ±5 minutes was considered too restrictive.

Section 6.2.2 Oleclumab preparation: Correction of typographical errors.

Table 3 Prohibited medications: Information on the rationale for the prohibition of EGFR TKIs added.

Section 8.4.5.1 Management of toxicity related to durvalumab and oleclumab combination therapy: Content of this section replaced by a cross-reference to the online durvalumab toxicity management guidelines.

Section 8.4.6 Adverse events of special interest: New section created for the AESIs for clarity.

Version 5.0, 19 March 2019

Key amendments and rationale for changes:

Table 1 Schedule of Activities – Treatment intervention period (Module 5):

- Clarified that tumour evaluation scans are required until objective disease progression, up to and including the 90-day safety follow-up period.
- Updated in line with the core protocol, to replace modified RECIST 1.1 with RECIST 1.1, to ensure comparability with other NSCLC study results. Updated for consistency across all modules of the study.

Figure 1 Study design: Updated to clarify that patients with locally advanced disease are included, and to specify ctDNA at pre-screening.

Section 2 Introduction and **Section 4.1 Overall design:** Amended in line with inclusion criterion 5 in the core clinical study protocol (CSP), which clarified the required prior treatment in response to questions from investigators. According to the study's main objective, patients must have had disease progression on a prior anti-PD-1/PD-L1 therapy. The patient must have also received a prior platinum doublet though it is not required to have had disease progression whilst receiving treatment with the platinum doublet therapy.

Section 2.1 Study rationale: Clarification that there is currently no established therapy for patients who have developed resistance to PD-1/PD-L1 and platinum-doublet therapies.

Section 2.2.1.1 Overview of durvalumab: Indication text updated to reflect status of approvals for durvalumab (IB Edition 14, 11 February 2019).

Section 2.2.1.2 Durvalumab data: PACIFIC overall survival data and Study CD-ON-MEDI4736-1108 efficacy data updated in line with the IB for durvalumab (IB Edition 14, 11 February 2019).

Section 2.2.2.4 Oleclumab data: New data included for Study D6070C00001; two new ongoing studies included: Study D6070C00004 and Study D6070C00005. Data in line with IB Edition 5.1, 11 January 2019.

Figure 2 Study flow diagram: Footnote added to specify that per protocol version 3.0, Module 4 (durvalumab + vistusertib) is closed to recruitment.

Table 2 Study drugs: Oleclumab dosage formulation description updated for consistency with durvalumab. 5% (w/v) dextrose IV bag removed from oleclumab description as oleclumab has not been tested in this type of bag.

Section 5.3.1 Restrictions applicable to durvalumab: Noted that topical corticosteroids are permitted.

The following sections have been updated in line with the core durvalumab Clinical Study Protocol (CSP), in which the Toxicity Management Guidelines (TMGs) for durvalumab have been removed from the main body of the CSP template and moved to a standalone annex. TMG versioning will be independent of the protocol allowing for consistency across the durvalumab clinical development programme. Updated for consistency across all modules of the study.

- Section 6.2.1 Durvalumab preparation and handling
- Section 6.2.2 Oleclumab preparation and handling

Section 6.2.1 Durvalumab preparation and handling: Updated for clarity and alignment with product insert.

Section 6.2.2 Oleclumab preparation and handling:

- Updated to clarify the observation time requirements before, during and after oleclumab infusion.
- Updated for clarity and consistency with durvalumab.

Section 6.2.3 Study drug administration: Updated in line with the core protocol, to replace modified RECIST 1.1 with RECIST 1.1, to ensure comparability with other NSCLC study results. **Section 6.4 Treatment compliance** and **Section 6.6 Dose modification and discontinuation:** Clarified that dose reductions are not allowed for durvalumab without prior agreement with the study physician. **Section 6.6 Dose modification and discontinuation:** Text changed from 'temporary discontinuation' to 'treatment interruption' for clarity. **Table 5 Schedule of Activities for patients re-allocated to second on-treatment period (Module 5):** Updated to clarify that informed consent and screening period to confirm eligibility for re-allocation will be performed within 28 days before dosing and to cross refer to the eligibility criteria in Table 1 of the core CSP.
Version 4.0, 26 October 2018
Updated version number to keep in line with changes made in the core CSP. No other changes were made in this appendix. Module 5 (HUDSON)
Version 3.1, 31 July 2018
Initial creation of Module 5. Version number 3.1 used for consistency with the rest of the protocol.

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

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1. PROTOCOL SUMMARY

1.1 Schedule of Activities (SoA)

The Schedule of Activities (SoA) for the on-treatment period for Module 5 is shown in Table 1 below, and for the optional re-allocated second on-treatment period in Section 7, Table 5. For the SoA for the pre-screening and main-screening visits, please refer to the core protocol.

Table 1 Schedule of Activities – Treatment intervention period (Module 5)

	C1 28 days Weeks 1-4		C2 28 days Weeks 5-8		C3 28 days Weeks 9-12	C4 28 days Weeks 13-16	C5 – etc All cycles 28 days	Study drug disc. (28 days after study drug disc)	Safety follow-up (90 days after study drug disc.)	Survival follow up	Notes
Week	**1**	**3**	**5**	**7**	**9**	**13**	**17, 21, 25, 29 etc**				
Cycle day	**1**	**15**	**1**	**15**	**1**	**1**	**1**				
Window (days)	**0**[a]	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±7**	**±7**	**±7**	
Study procedures[b]											
Physical examination	X	X	X	X	X	X	X	X			Section 8.2.2 (core protocol)
Vital signs	X	X	X	X	X	X	X	X			Section 8.2.3 (core protocol)
ECG	X	As clinically indicated									Section 8.2.4 (core protocol)
Concomitant medications	X	X	X	X	X	X	X	X			Section 6.5
Laboratory assessments[b]											
Clinical chemistry	X	X	X	X	X	X	X	X			Section 8.2.1 (core protocol). If screening laboratory assessments are performed within 3 days prior to Day 1 they do not need to be repeated at Day 1
Haematology	X	X	X	X	X	X	X	X			
APTT and INR		As clinically indicated									
TSH, free T_3, and free T_4	X	X	X	X	X	X	X	X			Section 8.2.1 (core protocol)
Urinalysis		As clinically indicated									Section 8.2.1 (core protocol)
Pregnancy test	X		X		X	X	X	X			Section 8.2.1.2 (core protocol)
AE/SAE assessment	X	X	X	X	X	X	X	X	X		Section 8.3 (core protocol)
Study drug administration[b]											
Durvalumab	X		X		X	X	X				Section 6.2.1
Oleclumab	X	X	X	X	X	X	X				Section 6.2.2
Drug accountability	X	X	X	X	X	X	X	X			Section 6.2.5

	C1 28 days Weeks 1-4		**C2** 28 days Weeks 5-8		**C3** 28 days Weeks 9-12	**C4** 28 days Weeks 13-16	**C5 – etc** All cycles 28 days	**Study drug disc.** (28 days after study drug disc)	**Safety follow-up** (90 days after study drug disc.)	**Survival follow up**	**Notes**
Week	**1**	**3**	**5**	**7**	**9**	**13**	**17, 21, 25, 29 etc**				
Cycle day	**1**	**15**	**1**	**15**	**1**	**1**	**1**				
Window (days)	**0[a]**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±7**	**±7**	**±7**	
Other assessments											
Blood for ctDNA assessments	X	X	X	X	X	X	X	X			Section 8.8 (core protocol)
Circulating soluble factors (plasma)	X	X	X			X		X			Section 8.8 (core protocol)
Whole blood for gene expression (PAXgene® RNA tubes)	X	X	X			X		X			Section 8.8 (core protocol)
PBMCs for flow cytometry (activation by PD-1 / CD8+)	X	X	X			X					Section 8.8 (core protocol)
TCR immuno-sequencing	X	X	X			X					Section 8.8 (core protocol)
Blood sample for ADA for durvalumab (pre-dose except at safety follow up)	X		X				X (C5D1) then Q12W in first year, then Q24W in second year		X		Section 8.5.3 (core protocol)
Tumour evaluation (CT or MRI) (RECIST 1.1)		Every 6 weeks ±1 week for the first 24 weeks relative to the date of first dose (Cycle 1 Day 1), then every 8 weeks ± 1 week thereafter, until objective disease progression as defined by RECIST 1.1 and confirmed with a subsequent scan (in the absence of clinically significant deterioration)									Section 8.1 (core protocol)
Biopsy on-treatment (mandatory)				X							Section 8.8 (core protocol). This should align with the first RECIST assessment.

	C1 28 days Weeks 1-4		**C2** 28 days Weeks 5-8		**C3** 28 days Weeks 9-12	**C4** 28 days Weeks 13-16	**C5 – etc** All cycles 28 days	**Study drug disc.** (28 days after study drug disc)	**Safety follow-up** (90 days after study drug disc.)	**Survival follow up**	**Notes**
Week	**1**	**3**	**5**	**7**	**9**	**13**	**17, 21, 25, 29 etc**				
Cycle day	**1**	**15**	**1**	**15**	**1**	**1**	**1**				
Window (days)	**0**[a]	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±7**	**±7**	**±7**	
Biopsy on disease progression (mandatory only for re-allocated patients)								X			Section 8.8 (core protocol)
Subsequent cancer therapy									X	X	Section 8.1.3.1 (core protocol). Every 3 months
Survival status										X[c]	Section 8.1.3.1 (core protocol). Every 3 months

[a] Every effort should be made to minimise the time between allocation to treatment and starting treatment. Note, if main screening assessments have been performed within 3 days prior to C1D1, then assessments do not need to be performed on C1D1 pre-dose.

[b] Following the final data cut-off for the module CSR (see Section 9.4.2 of the core protocol), any patients on study treatment may continue on treatment and should be assessed for safety according to standard local clinical practice. Study drug administration, SAE reporting and related safety assessment data should be recorded in the eCRF until 90 days after study drug discontinuation, when the patient will end participation in the study. The other assessments for the study will no longer be performed and those data will no longer be collected; the tumour evaluations will be performed as per standard of care. The survival follow-up will no longer be conducted.

[c] Ad hoc collection of survival status may be requested for overall survival analyses.

ADA Anti-drug antibodies; AE adverse event; APTT activated partial thromboplastin time; C cycle; CD8+ cytotoxic T cell; CSR clinical study report; CT computed tomography; ctDNA circulating tumour DNA; D day; ECG electrocardiogram; eCRF electronic Case Report Form; INR international normalised ratio; RECIST 1.1 Response Evaluation Criteria in Solid Tumours 1.1; MRI magnetic resonance imaging; PBMC peripheral blood mononuclear cell; PD-1 programmed cell death-1; Q12W every 12 weeks; Q24W every 24 weeks; SAE serious adverse event; TCR T-cell receptor repertoire; TSH thyroid-stimulating hormone; T_3 triiodothyronine; T_4 thyroxine.

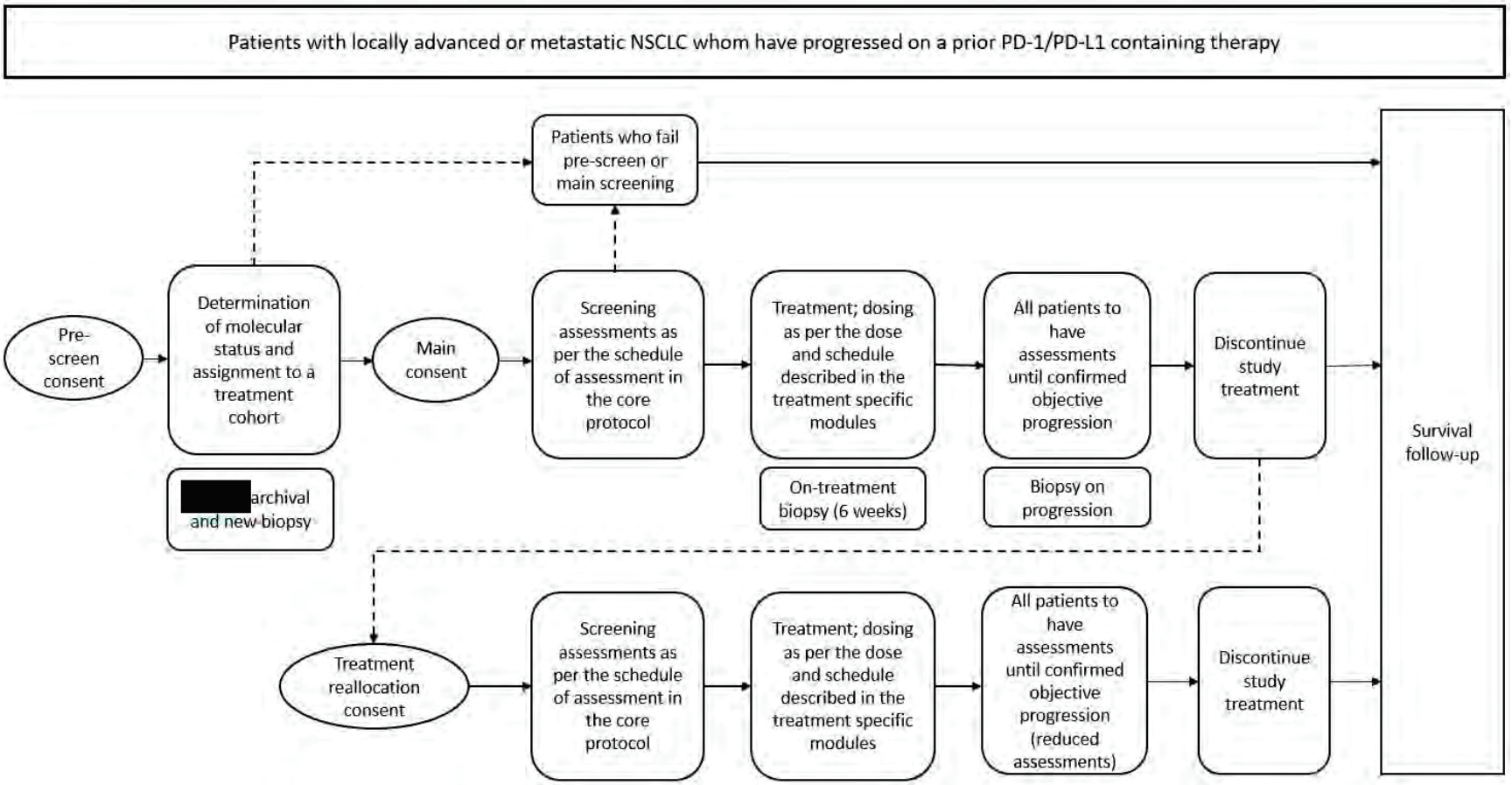
1.2 Synopsis

Please refer to Section 1.2 of the core protocol.

1.3 Schema

The general study design is summarised in Figure 1.

Figure 1 Study design



Note, from implementation of protocol v10.0, survival follow-up of screen failures and optional treatment re-allocation to a second treatment is no longer applicable.
ctDNA circulating tumour DNA; NSCLC non-small cell lung cancer; PD-1 programmed cell death-1; PD-L1 programmed cell death ligand 1.

2. INTRODUCTION

Study D6185C00001 (HUDSON) is a Phase II, open-label, multi-centre umbrella study in patients who have received an anti-programmed cell death-1 (PD-1)/anti-programmed cell death-ligand 1 (PD-L1) containing therapy and a platinum-doublet regimen for locally advanced or metastatic non-small cell lung cancer (NSCLC) either separately or in combination. The patient must have had disease progression on a prior line of anti-PD-1/PD-L1 therapy. The modular design allows the evaluation of the efficacy, safety, and tolerability of multiple study drugs. This module to the core study protocol describes Module 5, which will investigate the efficacy, safety, and tolerability of durvalumab administered in combination with oleclumab.

2.1 Study rationale

As described in Section 2.2 of the core protocol, immune checkpoint inhibitors targeting the PD-1/PD-L1 pathway have shown significant activity in the first- and second-line treatment settings in patients with NSCLC. However, it is becoming evident that there is a new and significant patient population emerging that does not respond to anti-PD-1/PD-L1 containing therapy (primary resistance) or progresses during anti-PD-1/PD-L1 containing therapy (acquired resistance). There is currently no established therapy for patients who have developed resistance to PD-1/PD-L1 and platinum-doublet therapies, and novel treatments for these patients are urgently needed.

The aim of this umbrella study (D6185C00001) is to investigate multiple study drugs for the treatment of NSCLC in molecularly matched and non-matched patient populations after failure of immune checkpoint inhibitors, to identify patient populations who may respond favourably to novel anti-tumour therapies.

2.2 Background

Durvalumab and oleclumab are both currently in clinical development as anti-cancer therapies in a variety of malignancies.

Durvalumab as a weight-based regimen of 10 mg/kg every 2 weeks (Q2W) has been approved for use in the treatment of patients with urothelial carcinoma (UC). On 16 February 2018, durvalumab was approved in the US for the treatment of patients with unresectable Stage III NSCLC. On 21 September 2018, durvalumab was approved in the European Union (EU) for the treatment of locally advanced, unresectable NSCLC in adults whose tumours express PD-L1 on ≥1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy. As of 12 July 2019, durvalumab is approved in over 45 countries for NSCLC. On 27 March 2020, the Food and Drug Administration approved durvalumab in combination with etoposide and either carboplatin or cisplatin as first-line treatment of patients with extensive-stage small cell lung cancer.

Module 5 will investigate both agents in combination, to test the hypothesis that the combination will result in complementary anti-tumour activity. Brief background on durvalumab and oleclumab, including their mechanisms of action, is provided below. For detailed descriptions of the chemistry, pharmacology, efficacy, and safety of durvalumab and oleclumab, refer to the respective Investigator's Brochures.

The study will recruit both biomarker-matched and biomarker non-matched patients (see Section 4.1). The biomarker of interest is cluster of differentiation (CD)73 expression as assessed using immunohistochemistry (IHC) (see Section 4.1). CD73 is a plasma membrane protein that catalyses the conversion of extracellular nucleotide monophosphates to nucleosides.

2.2.1 Durvalumab

2.2.1.1 Overview of durvalumab

Expression of PD-L1 protein is an adaptive immune response that helps tumours evade detection and elimination by the immune system. PD-L1 can be induced by inflammatory signals (eg, interferon-gamma) and can be expressed on both tumour cells and tumour-associated immune cells in tumour microenvironment. PD-L1 blocks T-cell function and activation through interaction with PD-1 and CD80 (B7.1). By binding to its receptors, PD-L1 reduces cytotoxic T-cell activity, proliferation, and cytokine production. Durvalumab is a fully human, high affinity, immunoglobulin (Ig) G1 kappa monoclonal antibody that selectively blocks the interaction of PD-L1 with PD-1 and cluster of differentiation (CD)80 (B7.1) while leaving PD-1/programmed cell death ligand-2 interaction intact. Durvalumab does not induce antibody dependent cell-mediated cytotoxicity. Selective blockade of PD-L1/PD-1 and PD-L1/CD80 interactions enhances antitumour immune responses. These antitumour responses may result in tumour elimination.

Durvalumab is approved in a number of territories including the US, EU, Japan, Canada and Brazil under the brand name IMFINZI™ Injection.

The recommended dose as per the IMFINZI package insert is 10 mg/kg administered as an IV infusion over 60 minutes every 2 weeks (Q2W).

For more information, please refer to the latest version of the Durvalumab Investigator's Brochure.

2.2.1.2 Durvalumab data

To date, durvalumab has been given to more than 12000 patients as part of ongoing studies either as monotherapy or in combination with other anticancer agents. Details on the safety profile of durvalumab monotherapy are summarized below. Refer to the current durvalumab IB for a complete summary of pre-clinical and clinical information including safety, efficacy, and pharmacokinetics (PK).

Clinical activity in locally advanced NSCLC

The efficacy of durvalumab was evaluated in the PACIFIC Study, a randomised, double-blind, placebo-controlled, multicentre study in 713 patients with histologically or cytologically confirmed locally advanced, unresectable NSCLC. Patients had completed definitive platinum-based chemoradiation within 1 to 42 days prior to initiation of the study and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Ninety-three percent of patients had received a total dose of 54 to 66 Gy of radiation. The study excluded patients who had progressed following concurrent chemoradiation therapy, patients with active or prior documented autoimmune disease within 2 years of initiation of the study; a history of immunodeficiency; a history of severe immune-mediated adverse reactions; medical conditions that required systemic immunosuppression, except physiological dose of systemic corticosteroids; active tuberculosis or hepatitis B or C or HIV infection or patients receiving live attenuated vaccine within 30 days before or after the start of durvalumab. Patients were randomised 2:1 to receive 10 mg/kg durvalumab (n=476) or 10 mg/kg placebo (n=237) via IV infusion Q2W for up to 12 months or until unacceptable toxicity or confirmed disease progression. Randomisation was stratified by gender, age (<65 years vs. ≥65 years) and smoking status (smoker vs. nonsmoker). Patients with disease control at 12 months were given the option to be re-treated upon disease progression. Tumour assessments were conducted every 8 weeks for the first 12 months and then every 12 weeks thereafter.

The demographics and baseline disease characteristics were well balanced between study arms. Baseline demographics of the overall study population were as follows: male (70%), age ≥65 years (45%), White (69%), Asian (27%), other (4%), current smoker (16%), past-smoker (75%), and never smoker (9%), World Health Organisation (WHO)/ECOG PS 0 (49%), WHO/ECOG PS 1 (50%). Disease characteristics were as follows: Stage IIIA (54%), Stage IIIB (44%), histological subgroups of squamous (47%), non-squamous (53%), PD-L1 expression in tumour cells (TC)≥25% (22%), PD-L1 expression TC<25% (41%). (PD-L1 status was retrospectively analysed using the Ventana PD-L1 [SP263] Assay in 451 patients with available samples, taken prior to concurrent chemoradiation therapy).

At the time of the interim progression-free survival (PFS) analysis, the median PFS by blinded independent central review (BICR) was significantly longer with durvalumab treatment (16.8 months) compared with placebo (5.6 months); hazard ratio 0.52; 98.9% CI: 0.39, 0.70; p<0.0001. At the time of the interim overall survival (OS) analysis, the median OS was not reached for the durvalumab arm and was 29.1 months for the placebo arm; hazard ratio, 0.69; 95% CI, 0.55, 0.86). The 36-month OS rate was 57.0% with durvalumab vs 43.5% with placebo.

Clinical activity in recurrent and metastatic NSCLC

Based on current data from the ongoing Study CD-ON-MEDI4736-1108 (NCT01693562), evidence of clinical activity with durvalumab has been observed. The following responses were observed in patients with NSCLC.

Overall, clinical activity was observed in both the PD-L1 high (defined as having tumour cells [TC] ≥25%) and PD-L1 low/negative (defined as TC <25%) subgroups, however, patients with PD-L1 high tumours had higher objective response rates (ORRs).

The ORR per [BICR] was 21.8% and 6.4% in patients with PD-L1 high and low/negative tumours, respectively and 15.3% in the overall population regardless of PD-L1 expression. The ORR was 25.9%, 14.3% and 11.5% in the 1L, 2L and 3L+ cohorts, respectively. Median duration of response (DOR) was 17.74 months. Median OS was 12.4 months; median OS was 21.0, 11.8 and 9.3 months in the 1L, 2L and 3L+ cohorts, respectively. The OS rate at 24 months was 29.6%.

The ATLANTIC study in third-line or higher NSCLC showed higher ORR and survival outcomes in high PD-L1 positive patients. Across cohorts the ORR ranged from 3 to 43%, median PFS ranged from 1.8 to 5.5 months and median OS ranged from 5.9 to 13.6 months but was not reached at the time of initial reporting in the >90% PD-L1 expressors. The ORR and survival outcomes reported in durvalumab studies are in keeping with other similar agents targeting the PD-1/PD-L1 axis (Garassino et al 2017).

Preliminary efficacy data from the MYSTIC study in first-line advanced or metastatic NSCLC showed that in PD-L1 high (≥25% TC) NSCLC, median PFS by BICR was 4.7 months for durvalumab monotherapy and 5.4 months for chemotherapy; hazard ratio of 0.87; 99.5% CI: 0.593, 1.285; p=0.324. The median OS was 16.3 months for the durvalumab arm and 12.9 months for the chemotherapy arm; hazard ratio for death was 0.76; 97.54% CI: 0.564, 1.019; p=0.036. The 24-month OS rate was 38.3% vs 22.7% and the 12-month PFS rate was 32.3% vs 14.3% for the durvalumab and chemotherapy arms respectively. When durvalumab was administered in combination with tremelimumab, the median PFS by BICR was 3.9 months for durvalumab + tremelimumab and 5.4 months for chemotherapy; hazard ratio of 1.05; 99.5% CI: 0.722,1.534; p=0.705. The median OS was 11.9 months for the durvalumab + tremelimumab arm and 12.9 months for the chemotherapy arm; hazard ratio for death was 0.85; 98.77% CI: 0.611, 1.173; p=0.202. The 24-month OS rate was 35.4% vs 22.7% and the 12-month PFS rate was 25.8% vs 14.3% for the durvalumab + tremelimumab and chemotherapy arms respectively.

Immuno-oncology agents targeting the PD-1/PD-L1 pathway have demonstrated activity as monotherapy and in combination with chemotherapy in patients who are immunotherapy-naïve. However, the present study will recruit patients who either have primary resistance to

anti-PD-1/PD-L1 therapy or who developed acquired resistance while on anti-PD-1/PD-L1 therapy. Thus, in this immunotherapy-resistant setting, durvalumab will be administered in combination with an agent that has a different and complementary mechanism of action in order to maximise the likelihood of clinical activity.

2.2.2 Oleclumab

2.2.2.1 Rationale for targeting CD73 and clinical development of oleclumab

Immune responses directed against malignant tumours are one of the body's natural defences against the development and proliferation of cancer cells. However, immune cell function may be repressed via activation of multiple immunosuppressive mechanisms. This allows tumour escape from immune surveillance and subsequent growth and metastasis.

Adenosine is an autocrine and paracrine regulatory factor that accumulates in the tumour microenvironment, influencing immune activity, angiogenesis, and metastasis (Antonioli et al 2013). Adenosine is produced through enzymatic dephosphorylation of adenosine monophosphate (AMP) by 5'-nucleotidase. In the extracellular space, CD39 and CD73 in tandem metabolize adenosine triphosphate to AMP, and AMP to adenosine, respectively, and are a major source of extracellular adenosine. The rate-limiting step in the generation of extracellular adenosine is the dephosphorylation of AMP by CD73. Adenosine in turn induces intracellular signalling via binding to adenosine receptors expressed on various cell types (Sadej et al 2006; Spychala et al 2004; Wang et al 2008; Zhang 2010). Adenosine has multiple "tumour protective" effects, including stimulation of tumour growth and angiogenesis, and inhibition of cytokine synthesis, adhesion of immune cells to the endothelial wall, and the suppression of effector T-cells, macrophages, and natural killer cells (Spychala 2000).

Overexpression of CD73 is an independent biomarker for predicting poor survival in patients with NSCLC (Inoue et al 2017). The high level of CD73 on tumour cells is functionally linked to an immunosuppressive tumour microenvironment (Young et al 2016).

2.2.2.2 Overview of oleclumab

Oleclumab is a human Ig G1 lambda monoclonal antibody that selectively binds to and inhibits the ectonucleotidase activity of CD73. The triple mutation, L234F/L235E/P331S (according to European Union numbering convention), is encoded in the heavy chain constant region to significantly reduce IgG effector function. Oleclumab inhibits the catalysis of AMP to adenosine and inorganic phosphate by CD73. Extracellular adenosine contributes to the immunosuppressive effects of both regulatory T cells and myeloid-derived suppressor cells, among others (Antonioli et al 2013). The enzymatic blockade of CD73 caused by binding of oleclumab to CD73 may lead to increased antitumour immunity.

2.2.2.3 Rationale for oleclumab in combination with durvalumab

This Module explores the combination of anti-CD73 and anti-PD-L1 therapies in patients who failed prior PD-1 or PD-L1 therapy and also have received platinum-based doublet chemotherapy. Based upon the clinical finding that CD73 expression portends worse prognosis in NSCLC, mechanism of action and supportive preclinical data, the addition of CD73 antagonist oleclumab may increase response rates, overcome resistance and improve response duration when compared to monotherapy PD-1 or PD-L1 inhibition.

In murine cancer models, targeting cancer cell CD73 using RNA interference inhibits tumour growth by direct inhibition of tumour cell migration and metastasis (Zhi et al 2007) and by freeing antitumour T cells from the suppressive effects of extracellular adenosine, restoring efficacy of adoptive T-cell therapy (Jin et al 2010). In a variety of mouse tumour models, CD73 antagonist antibodies show antitumour responses, especially in tumour types with high levels of CD73 expression (Stagg et al 2010).

2.2.2.4 Oleclumab data

As of 09 June 2019, a total of 289 subjects had been enrolled across 8 clinical studies with oleclumab. Interim data are available for 3 studies: Study D6070C00001, Study D6070C00004, and Study D6070C00005.

Study D6070C00001 is a first-time-in-human, Phase I, multicentre, open-label, dose-escalation, and dose-expansion study of oleclumab administered as a single agent or in combination with durvalumab in adult subjects with selected advanced solid tumours (microsatellite stable colorectal cancer, pancreatic adenocarcinoma [Panc], and epidermal growth factor receptor mutant non-small cell lung cancer [EGFRm NSCLC]). In this study subjects received oleclumab at doses of 5, 10, 20, and 40 mg/kg given IV Q2W as monotherapy and in combination with durvalumab 10 mg/kg Q2W in the dose escalation phase. As of the data cut-off, the monotherapy and combination therapy dose-escalation phases were completed with a total enrolment of 42 and 24 subjects, respectively. The combination therapy dose-expansion phase was ongoing, at the recommended Phase II dose of 40 mg/kg oleclumab + 10 mg/kg durvalumab, with a total of 111 subjects enrolled.

Study D6070C00004 is an ongoing multi-arm, open-label, multicentre, Phase 1b/2 study to evaluate novel combination therapies in subjects with previously treated advanced EGFRm NSCLC. The study consists of 2 parts, dose escalation and dose expansion. There are currently 2 arms: oleclumab (1500 or 3000 mg Q2W) + osimertinib (80 mg QD) (Arm A), and oleclumab (1500 or 3000 mg Q2W) + AZD4635 (25, 50, 75 or 100mg QD) (Arm B). As of the data cut-off, 11 subjects have been treated in Arm A and 14 subjects in Arm B.

Study D6070C00005 is an ongoing Phase 1b/2, multicentre, open-label, dose-escalation and dose-expansion study to assess the safety, preliminary antitumor activity, immunogenicity, and PK of oleclumab with or without durvalumab in combination with chemotherapy

administered in subjects with first-line (Cohort A) or second-line (Cohort B) metastatic pancreatic adenocarcinoma (PDAC). As of the data cut-off, a total of 75 subjects had been dosed in the dose-escalation and expansion cohorts: 14 subjects were dosed in dose-escalation Cohort A (oleclumab 1500 or 3000 mg + durvalumab + gemcitabine + nab-paclitaxel), 11 subjects in dose-escalation Cohort B (oleclumab 1500 or 3000 mg + durvalumab + mFOLFOX) and 50 subjects in dose-expansion Cohort A (A1: gemcitabine + nab-paclitaxel; A2: oleclumab 3000 mg + gemcitabine + nab-paclitaxel; A3: oleclumab 3000 mg + durvalumab + gemcitabine + nab-paclitaxel).

Safety - oleclumab monotherapy

In the monotherapy dose escalation phase of Study D6070C00001, 39 of 42 subjects (92.9%) with advanced CRC and pancreatic cancer experienced ≥1 treatment-emergent adverse event (TEAE) and 23 subjects (54.8%) experienced a treatment-related AE. The most frequently reported TEAEs (in ≥15% of all subjects) were fatigue (40.5%), anaemia (23.8%), abdominal pain (23.8%), dyspnoea (21.4%), decreased appetite (21.4%), vomiting (19.0%), and pyrexia (16.7%). Three subjects experienced treatment-related Grade 3 or 4 AEs of amylase increased, gamma glutamyltransferase (GGT) increased, lipase increased, and hyperglycaemia. There were no clinically meaningful trends in incidence of TEAEs across dose groups. The most frequently reported treatment-related AEs (≥5% total subjects) were fatigue (16.7%), nausea and anaemia (9.5% each).

Overall, 15 subjects (35.7%) experienced serious adverse events (SAEs). Three subjects (7.1%) experienced the SAE of ascites; this was the only SAE reported by more than one subject. There were no treatment-related SAEs or treatment-related AEs leading to discontinuation. One subject died due to an AE of small intestinal obstruction considered unrelated to oleclumab. There were no dose-limiting toxicities (DLTs) reported in the oleclumab monotherapy dose-escalation phase, and the maximum tolerated dose (MTD) was not reached.

Safety - oleclumab in combination with durvalumab

Study D6070C00001

Twenty-four subjects with advanced pancreatic and colorectal cancer were treated with oleclumab + durvalumab combination therapy in the dose-escalation phase. All 24 subjects experienced AEs, and 54.2% of subjects experienced treatment-related AEs. The most frequently reported AEs (in ≥15% of total subjects, regardless of causality) were fatigue (29.2%), vomiting (29.2%), abdominal pain (20.8%), and nausea (16.7%). Treatment-related Grade 3 or 4 AEs occurred in 5 (20.8%) of subjects; aspartate aminotransferase (AST) increased (2 subjects) was the only treatment-related Grade 3 or 4 AE reported in >1 subject. Ten subjects (41.7%) experienced SAEs. Pulmonary embolism (2 subjects) was the only SAE experienced by more than 1 subject. One subject reported a treatment-related SAE of

thrombocytopenia. Two subjects discontinued treatment due to AEs of AST increased, ALT increased, blood ALP increased and blood bilirubin increased. One of the 2 subjects experienced events that were considered by the investigator to be treatment-related (AST increased and blood bilirubin increased). Five of the 24 subjects (20.8%) experienced at least one AESI. Peripheral oedema and pulmonary embolism were the only AESIs reported in >1 subject (2 subjects each). One subject had a fatal AE of renal failure considered unrelated to study treatment by the investigator. There were no DLTs reported during the oleclumab + durvalumab combination therapy dose-escalation phase, and the MTD was not reached.

Overall, 111 subjects with colorectal, pancreatic, and NSCLC were treated with 40 mg/kg oleclumab Q2W + 10 mg/kg durvalumab Q2W combination therapy in the dose-expansion phase of the study. Of the 111 subjects, 93.7% of subjects experienced AEs, and 59 (53.2%) of subjects experienced treatment-related AEs. The most frequently reported AEs (≥15% of subjects, regardless of causality) were fatigue (28.8%), nausea (18.9%), abdominal pain and vomiting (18.0% each), constipation (17.1%) AST increased (16.2%), and pyrexia and diarrhoea (15.3% each). Treatment-related Grade 3 or 4 AEs were reported in 15.3% of subjects; hepatitis, AST increased, blood alkaline phosphatase (ALP) increased, and lipase increased occurred in 2 subjects each. Treatment-related SAEs were reported in 7.2% of subjects; hepatitis (2 subjects) was the only treatment-related SAE reported in >1 subject. Four subjects reported treatment-related AEs leading to discontinuation; hepatitis was reported in 2 of the subjects, fatigue was reported in the third, and systemic inflammatory response syndrome (SIRS) was reported in the fourth. Twenty five of the 111 subjects (22.5%) reported at least one AESI. The most common AESIs (≥ 2% of expansion total) reported were peripheral oedema (10.8%), pulmonary embolism (6.3%) and deep vein thrombosis (3.6%).

In the oleclumab + durvalumab combination therapy dose-expansion phase, 3 subjects had AEs leading to death. Of the 3 subjects that had AEs leading to death, 1 subject died of a treatment-related SAE of SIRS, and the other 2 subjects had fatal AEs of respiratory arrest, and pulmonary embolism that were considered unrelated to study treatment.

Study D6070C00004

All 11 subjects treated in the dose-escalation portion of Arm A (oleclumab + osimertinib) experienced AEs. The most frequently reported AEs (≥10% of total subjects) were paronychia (45.5%), diarrhoea (36.4%), stomatitis (27.3%), fatigue, dyspnoea, urticaria, hyponatraemia, neutropenia, and decreased appetite (18.2% each). Eight (72.7%) subjects had oleclumab-related events. Most of the oleclumab-related AEs were reported in 1 subject each; decreased appetite was the only event that was reported in 2 of the 11 subjects (18.2%). SAEs of haemorrhage (Grade 3), pneumonia (Grade 3), spinal cord compression (Grade 4), pleural effusion (Grade 3), and hyponatremia (Grade 3) were reported in 4 subjects; none of the SAEs were considered to be treatment-related. One subject discontinued treatment due to

"drug-induced pneumonitis" (verbatim term) and the event was considered to be oleclumab- and osimertinib-related. Three subjects (27.3%) reported AESIs for oleclumab, which included anaphylactic reaction (1 subject), infusion related reaction (1 subject) and urticaria (2 subjects). No DLTs were reported. One subject died while on treatment and it was due to disease under treatment.

Eleven of the 14 subjects in Arm B (oleclumab + AZD4635) had AEs. Across the 3 dose levels, the most common AEs reported (≥ 10% of the total subjects) were nausea (50.0%), vomiting (42.9%), headache (35.7%), constipation (28.6%), dyspnoea and fatigue (21.4% each), anaemia, back pain, dizziness and non-cardiac chest pain (14.3%) each. Six subjects experienced oleclumab-related events; the most common (≥10% in total) were nausea (35.7%), fatigue (21.4%) and vomiting (14.3%).

Five subjects reported 6 SAEs: liver abscess (Grade 3), back pain (Grade 3), headache (Grade 3), dyspnoea (Grade 5), pulmonary embolism (Grade 3) and respiratory arrest (Grade 4). Only the event of pulmonary embolism was considered to be oleclumab-related.

One subject had 2 DLTs (Grade 1 vomiting considered unrelated to both oleclumab and AZD4635, and an SAE of Grade 3 pulmonary embolism, considered related to both oleclumab and AZD4635 the pulmonary embolism led to omission of both oleclumab and AZD4635. A second subject experienced treatment-related AEs of nausea and vomiting that resulted in treatment discontinuation.

Two subjects (14.3%) reported AESIs: infusion related reaction (Grade 1) considered by the investigator as related to oleclumab, and pulmonary embolism (Grade 3) considered by the investigator as related to oleclumab and AZD4635. There were no fatal AEs. Three subjects (21.4%) died during the study due to disease under treatment. Of the 3 subjects, 2 subjects died while on treatment.

Efficacy

Preliminary efficacy data are available from Study D6070C00001 (combination therapy extension). The confirmed ORR in the CRC, Panc, and NSCLC expansion cohorts were 2.4% (95% CI: 0.1%, 12.6%), 4.8% (95% CI: 0.6%, 16.2%), and 11.1% (1.4%, 34.7%), respectively. The disease control rate (DCR) in the CRC, Panc, and NSCLC expansion cohorts was 21.4%, 23.8%, and 18.5%, respectively. The median progression free survival (PFS) in the CRC, Panc, and NSCLC expansion cohorts was 1.8, 1.8, and 1.7 months, respectively. The median overall survival (OS) in the CRC, Panc, and NSCLC expansion cohorts was 7.0, 6.3 and 5.3 months, respectively.

In Study D6070C00004 (oleclumab + osimertinib arm [Arm A]), the confirmed ORR in the total group was 27.3%. The DCR in the total group was 81.8%. In Arm B (oleclumab +

AZD4635), there was no objective response as of the data cut-off. One subject (7.1%) from dose level group 1 (oleclumab 1500 mg Q2W + AZD4635 50 mg QD) had stable disease.

Pharmacokinetics

As of 06 March 2019, PK data were available for a total of 170 subjects following treatment with oleclumab 5 to 40 mg/kg once Q2W administered either as a monotherapy (n=42) or in combination with durvalumab at 10 mg/kg Q2W (n=128). Oleclumab appeared to exhibit a nonlinear PK at the lowest dose of oleclumab 5 mg/kg as most evident in trough concentrations and exhibited linear PK at doses of oleclumab 10 mg/kg and higher in both monotherapy and combination therapy groups. Serum exposures were similar when oleclumab was administered either alone or in combination with durvalumab. The PK exposures (trough plasma concentration [C_{trough}]) increased in a more than proportional manner from oleclumab 5 to 10 mg/kg and in an approximately dose-proportional manner from oleclumab 10 to 40 mg/kg. Accumulation of oleclumab was observed following repeated dosing. Population PK analysis indicated only moderate impact of body weight on PK of oleclumab (coefficient of ≤0.5 on systemic clearance and volume of distribution), however, change expected in PK parameters due to body weight was not significant at approximately 30%. Fixed doses of 1500 mg and 3000 mg were selected to approximate 20 and 40 mg/kg, respectively, based on the median body weight of 75 kg. Complete suppression of free soluble CD73 was observed following administration of oleclumab either as monotherapy or in combination therapy. Free serum soluble CD73 levels were below the limit of detection (0.25 ng/mL) in the majority of subjects at all times after the first dose of oleclumab.

Dose selection

Based on analysis of safety, PK, and preliminary efficacy in Study D6070C00001, a recommended phase 2 fixed dose of 3000 mg (equivalent to 40 mg/kg) by IV infusion Q2W for 2 cycles, and every 4-weeks (Q4W) thereafter (see Section 4.3.2).

2.3 Benefit/risk assessment

2.3.1 Potential benefit of oleclumab in combination with durvalumab

Inhibition of PD-L1 and PD-1 pathway has elicited durable antitumour responses and long-term remission in a subset of patients with a broad spectrum of cancers (Zou et al 2016). As summarised in Section 2.2.1.2, durvalumab treatment alone has proven benefit in patients with Stage III NSCLC when given after chemoradiotherapy and has resulted in objective responses in patients with locally advanced and metastatic NSCLC. Preclinical experiments have shown increased tumour growth inhibition and survival in tumour bearing mice treated with anti-CD73 antibody in combination with anti-PD-1/PD-L1 antibodies. Based upon the mechanism of action, supportive pre-clinical data, and early indication of anti-tumour activity in the Phase I/Ib study (Study D6070C00001), the combination therapy with oleclumab and durvalumab

may increase response rates and improve response duration in patients with NSCLC when compared to monotherapy of either agent.

2.3.2 Potential risks of oleclumab in combination with durvalumab

Toxicities common to any immunoglobulin include important potential risks of infusion-related reactions, hypersensitivity (anaphylaxis and serious allergic reactions), and immune complex disease. Administration of 2 immunoglobulins (durvalumab and oleclumab) therefore may increase the risk of such events being experienced by the patients. Additional potential risks considered to be specifically associated with administration of oleclumab based on the mechanism of action include arterial and joint calcifications, arterial ischemic disorder and important potential risks of increased microvascular permeability and thrombosis. Other potential risks associated with any IV administration are localised infection, redness, swelling, pain, and induration at the administration site.

2.3.3 Overall benefit/risk assessment

As described in Section 2.3 of the core protocol, patients recruited to this study are not expected to have other treatment options apart from single agent chemotherapy (± ramucirumab), such as docetaxel. The survival outcome and toxicity profile of chemotherapy in this setting mean that other active therapies are highly desirable and present a potential advantage for patients.

The study design aims to identify patient populations who may respond favourably to novel anti-tumour therapies. Based upon the available non-clinical and clinical safety data, the limited survival benefit provided by the currently available treatment options to patients, the limited life expectancy due to malignant disease, and the hypothesis of the complementary effect of the 2 agents, the investigation of the potential therapeutic efficacy of the combination of durvalumab with oleclumab in patients with advanced or metastatic NSCLC is acceptable, and the overall benefit/risk assessment supports the proposed study design. A proposed benefit to seeking signals by this biomarker stratification strategy includes the opportunity to discover potential increased sensitivity to the study drugs under evaluation.

3. OBJECTIVES AND ENDPOINTS

Please refer to the core protocol.

4. STUDY DESIGN

4.1 Overall design

This is an open-label, multi-centre, umbrella study in patients who have received an anti-PD-1/PD-L1 containing therapy and a platinum-doublet regimen for locally advanced or metastatic NSCLC either separately or in combination. The patient must have had disease

progression on a prior line of anti-PD-1/PD-L1 therapy. For an overview of the study design see Figure 1; further details on the overall design are provided in Section 4 of the core protocol. For details on the study drugs given in Module 5, see Section 6.1 of this module.

Module 5 will evaluate the efficacy, safety, and tolerability of durvalumab (given IV) at 1500 mg Q4W in combination with oleclumab given IV at 3000 mg Q2W for 2 cycles and then Q4W thereafter in 3 cohorts of patients: 1 biomarker-matched and 2 biomarker non-matched cohorts, as follows:

- Cohort A.5.73H will investigate durvalumab in combination with oleclumab in patients with high expression of CD73. For details of the IHC assay and staining please refer to the Pathology and Genomics Manual.
- Cohorts B.5 will investigate durvalumab in combination with oleclumab, stratified by prior response to immunotherapy; primary resistance (Cohort B.5.PRI), or acquired resistance (Cohort B.5.ACQ). These terms are defined as follows:
  - Primary resistance; patients who had anti-PD-1/PD-L1 containing therapy but had progression of disease (PD) within ≤24 weeks from the start of treatment.
  - Acquired resistance; patients who had progressive disease >24 weeks from the start of anti-PD-1/PD-L1 containing therapy whilst still on that treatment.

NOTE: Cohort B.5.PRI has closed recruitment early, as per core protocol Section 9.2, due to lack of positive efficacy data from the other 2 cohorts in the module that have completed enrolment.

A study flow diagram is provided in the core protocol (Figure 4).

4.2 Scientific rationale for Module 5

The study aims to identify patient populations who may respond favourably to novel anti-tumour therapies, and the modular design allows evaluation of the efficacy, safety, and tolerability of multiple study drugs. The study requires an open-label design owing to the different schedules and routes of administration of the study drugs.

The scientific rationale for exploring the safety, tolerability, and anti-tumour activity of durvalumab in combination with oleclumab in patients with metastatic NSCLC within this study is detailed in Section 2.2.2.3.

4.2.1 Scientific rationale for inclusion of biomarker-matched and biomarker non-matched cohorts

The scientific background for inclusion of biomarker-matched and biomarker non-matched cohorts in Module 5 is as follows.

In situ protein expression levels of CD73 will be used for allocation of patients. High tumoural CD73 expression levels are associated with a poor prognosis in patients with NSCLC. The inclusion of non-matched arms including patients with a lower level of CD73 for treatment with durvalumab in combination with oleclumab will permit both the validation of the current CD73 IHC cut-off as well as the testing of patients who might have low tumoural CD73 and/or varying levels of CD73 expression within the stroma or tumour infiltrating leukocytes.

Cohort A.5.73H (biomarker-matched: CD73 high): Elevated levels of extracellular adenosine have been reported within the tumour microenvironment, in part due to upregulation of CD73 and the accompanied increased enzymatic activity within cancerous tissues (Zhang 2010). Inhibition of CD73 results in enhanced antitumour activity by disrupting adenosine-mediated immune suppression effect. Immune checkpoint blockade by durvalumab at the same time is expected to overcome the inhibitory action of PD-L1 on T-cell activation.

Cohorts B.5.PRI and B.5.ACQ (biomarker non-matched: primary resistance; acquired resistance): Expression levels and functional role of CD73 may differ in tumours with primary and acquired resistance to PD-1/PD-L1 blockade and therefore the response to the treatment combination of durvalumab and oleclumab may also differ in these populations. Checkpoint blockade at the same time by durvalumab is expected to overcome the inhibitory action of PD-L1 on T-cell activation.

4.3 Justification for dose

4.3.1 Justification for durvalumab dose

A durvalumab dose of 20 mg/kg Q4W is supported by in vitro data, pre-clinical activity, clinical PK/pharmacodynamics, biomarkers, and activity data from Study CD-ON-MEDI4736-1108 (hereafter referred to as Study 1108) in patients with advanced solid tumours and from a Phase I study performed in Japanese patients with advanced solid tumour (D4190C00002).

PK/Pharmacodynamic data

Based on available PK/pharmacodynamic data from ongoing Study 1108 with doses ranging from 0.1 to 10 mg/kg Q4W or 15 mg/kg Q4W, durvalumab exhibited non-linear (dose dependent) PK consistent with target-mediated drug disposition. The PK approached linearity at ≥3 mg/kg Q4W, suggesting near complete target saturation (membrane-bound and sPD-L1), and further shows that the durvalumab dosing frequency can be adapted to a particular regimen given the linearity seen at doses higher than 3 mg/kg. The expected half-life with doses ≥3 mg/kg Q4W is approximately 21 days. A dose-dependent suppression in peripheral sPD-L1 was observed over the dose range studied, consistent with engagement of durvalumab with PD-L1. A low level of immunogenicity has been observed. No patients have experienced

immune-complex disease following exposure to durvalumab. (For further information on immunogenicity, please see the current durvalumab IB).

A population PK model was developed using the data from Study 1108 (doses=0.1 to 10 mg/kg Q2W or 15 mg/kg Q4W; Fairman et al 2014). Multiple simulations indicate that a similar overall exposure is expected following both 10 mg/kg Q4W and 20 mg/kg Q4W regimens, as represented by AUC_{ss} (4 weeks). Median $C_{max,ss}$ is expected to be higher with 20 mg/kg Q4W (~1.5 fold) and median $C_{trough,ss}$ is expected to be higher with 10 mg/kg Q4W (~1.25 fold). Clinical activity with the 20 mg/kg Q4W dosing regimen is anticipated to be consistent with 10 mg/kg Q4W with the proposed similar dose of 20 mg/kg Q4W expected to (a) achieve complete target saturation in majority of patients; (b) account for anticipated variability in PK, pharmacodynamics, and clinical activity in diverse cancer populations; (c) maintain sufficient PK exposure in case of ADA impact; and (d) achieve PK exposure that yielded maximal antitumour activity in animal models.

Given the similar area under the serum drug concentration-time curve (AUC) and modest differences in median peak and trough levels at steady state, the observation that both regimens maintain complete sPD L1 suppression at trough, and the available clinical data, the 20 mg/kg Q4W and 10 mg/kg Q4W regimens are expected to have similar efficacy and safety profiles, supporting further development with a dose of 20 mg/kg Q4W.

Clinical data

Refer to the current durvalumab IB for a complete summary of clinical information including safety, efficacy, and PK at the 20 mg/kg Q4W regimen.

Rationale for fixed dosing

A population PK model was developed for durvalumab using monotherapy data Study 1108 (N=292; doses = 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W; solid tumors). Population PK analysis indicated only minor impact of body weight on the PK of durvalumab (coefficient of ≤0.5). The impact of body weight-based (10 mg/kg Q2W) and fixed dosing (750 mg Q2W) of durvalumab was evaluated by comparing predicted steady state PK concentrations (5th, median, and 95th percentiles) using the population PK model. A fixed dose of 750 mg was selected to approximate 10 mg/kg (based on median body weight of ~75 kg). A total of 1000 patients were simulated using body weight distribution of 40 to 120 kg. Simulation results demonstrate that body weight-based and fixed dosing regimens yield similar median steady state PK concentrations with slightly less overall between-patient variability with fixed dosing regimen.

Similar findings have been reported by others (Narwal et al 2013, Ng et al 2006, Wang et al 2009, Zhang et al 2012). Wang and colleagues investigated 12 monoclonal antibodies and found that fixed and body size-based dosing perform similarly, with fixed dosing being better

for 7 of 12 antibodies (Wang et al 2009). In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-patient variability in PK/pharmacodynamic parameters (Zhang et al 2012).

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar PK exposure and variability, AstraZeneca considered it feasible to switch to fixed dosing regimens. Based on average body weight of 75 kg, a fixed dose of 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) is included in the current study.

An exception to 1500 mg fixed dosing is made for patients with low body weight (below 30 kg). Patients with a body weight of 30 kg or less must receive weight-based dosing, equivalent to 20 mg/kg, until weight increases to greater than 30 kg. At this time, fixed dosing data for patients weighing below 30 kg (corresponding to doses greater than 50 mg/kg) are not available and are not yet supported by product development.

Thus, the clinical activity observed coupled with the safety profile, translational science correlates, and non-clinical data supports further development with a dose of 1500 mg Q4W. The dose of durvalumab will not be modified during the study.

4.3.2 Justification for oleclumab dose

The oleclumab dose of 3000 mg Q2W for 2 cycles, followed by 3000 mg Q4W, was selected based on the available clinical safety, tolerability, efficacy, and PK data from the ongoing Phase I Study D6070C00001. In this study doses of 5, 10, 20 and 40 mg/kg Q2W were examined both as a monotherapy and in combination with durvalumab 10 mg/kg Q2W. Oleclumab was well tolerated and there were no observed dose-limiting toxicities either as monotherapy or in combination with durvalumab (Section 2.2.2.4). The oleclumab 40 mg/kg Q2W dose (equivalent to the oleclumab 3000 mg Q2W fixed dose for a 75 kg individual) was identified for evaluation with durvalumab 10 mg/kg Q2W in the dose-expansion phase of Study D6070C00001.

The target dose of 3000 mg Q2W for 2 cycles was chosen with the intent to achieve exposures for the initial 70 days similar to those observed at 40 mg/kg Q2W dose in Study D6070C00001 where clinical activity has been observed and CD73 is expected to have been inhibited maximally. Subsequently, a Q4W schedule at 3000 mg is predicted to result in adequate long-term exposures with the predicted median trough of 84 µg/mL. The predicted trough concentration is above the estimated CD73 saturating concentration of approximately 40 µg/mL (100-fold of estimated Michaelis-Menten constant from the population PK model) to maintain optimal CD73 saturation at steady state.

The rationale for a fixed-dosing regimen is the same as outlined above for durvalumab (Section 4.3.1)

Thus, based on an average body weight of 75 kg, a fixed dose of oleclumab 3000 mg Q2W (equivalent to 40 mg/kg Q2W) for 2 cycles followed by Q4W is included in Module 5.

4.4 End of study definition

Please refer to the core protocol.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

Each patient should meet all the inclusion criteria and none of the exclusion criteria for this study in order to be assigned to a study cohort. Under no circumstances can there be exceptions to this rule. Patients who do not meet the entry requirements are screen failures; refer to Section 5.4 of the core protocol.

5.1 Inclusion criteria (Module 5-specific)

Patients are eligible to be included in the study only if all the following inclusion criteria apply. Please also refer to Section 5.1 of the core protocol for the inclusion criteria applicable to all modules in the study. Additional inclusion criteria applicable to Module 5 only are described in this section.

M-1 Patients must fulfil all the core eligibility criteria.

M-2 Body weight ≥35 kg.

5.2 Exclusion criteria (Module 5-specific)

Patients must not enter Module 5 of the study if any of the following exclusion criteria apply. Please also refer to Section 5.2 of the core protocol for the exclusion criteria applicable to all modules in the study. Additional exclusion criteria applicable to Module 5 only are described in this section.

M-1 Patients meet any of the core exclusion criteria.

M-2 History of venous thrombosis within the past 3 months.

M-3 Inadequate organ function:

- Absolute neutrophil count <1.5 x 10^9/L
- Platelet count (see core protocol exclusion 18b)
- Haemoglobin (see core protocol exclusion 18c)
- AST and ALT >2.5 x ULN (>5 x ULN in the presence of liver metastases), but cannot be associated with concurrent elevated bilirubin

- Total bilirubin (see core protocol exclusion 18e)
- Creatine clearance (see core protocol exclusion 18f)
- Albumin <3.0 g/dL.

M-4 History of solid organ transplantation.

M-5 Uncontrolled intercurrent bleeding diatheses (see core protocol exclusion 4 for a list of other uncontrolled intercurrent illnesses considered as exclusions).

For procedures for withdrawal of incorrectly enrolled patients see Section 7.3 of the core protocol.

5.3 Lifestyle restrictions

5.3.1 Restrictions applicable to durvalumab and oleclumab

Patients should not donate blood or blood components while participating in this study and through 90 days after receipt of the final dose of durvalumab or until alternate anticancer therapy is started.

Immunosuppressive medications including, but not limited to systemic corticosteroids at doses beyond 10 mg/day of prednisone or equivalent, methotrexate, azathioprine and tumour necrosis factor alpha blockers are prohibited. Use of immunosuppressive medications for the management of study drug-related AEs and in patients with contrast allergies is acceptable. In addition, use of topical, inhaled and intranasal corticosteroids is permitted (see Table 3).

Live attenuated vaccines within 30 days of durvalumab and oleclumab dosing (ie, 30 days prior to the first dose, during treatment and for 180 days post-discontinuation of both drugs). Inactivated viruses, such as those in the influenza vaccine, are permitted (see Table 3).

Reproduction

Please refer to section 5.3 of the core protocol.

5.4 Screen failures

Please refer to Section 5.4 of the core protocol.

6. STUDY TREATMENTS

Study treatment is defined as any study drug(s) (including marketed product comparator and placebo) or medical device(s) intended to be administered to a study participant according to the study protocol. Study treatment in Module 5 refers to durvalumab and oleclumab.

6.1 Treatments administered

6.1.1 Study drugs

Table 2 Study drugs

Study drug name:	Oleclumab	Durvalumab
Dosage formulation:	Supplied as a vialed liquid solution containing 500 mg (nominal) oleclumab per vial. The solution contains 50 mg/mL oleclumab, 25 mM histidine/histidine hydrochloride, 240 mM sucrose, 0.03% (w/v) polysorbate 80, at pH 6.0. The nominal fill volume is 10.0 mL	Supplied as a vialed liquid solution containing 500 mg (nominal) durvalumab per vial. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine hydrochloride, 275 mM trehalose dihydrate, 0.02% (w/v) polysorbate 80, at pH 6.0. The nominal fill volume is 10.0 mL
Route of administration	IV infusion	IV infusion
Dosing instructions: Please refer to Section 6.2 for study specific handling instructions	Oleclumab 3000 mg via IV infusion Q2W ±2 days for 2 cycles, and then Q4W ±2 days thereafter (fixed dosing for patients >30 kg body weight)	Durvalumab 1500 mg via IV infusion Q4W ±2 days (fixed dosing for patients >30 kg body weight)
Packaging and labelling	Study drug will be provided in vials. Each vial will be labelled in accordance with GMP Annex 13 and per country regulatory requirement. Labels will be prepared in accordance with GMP and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language, as required. Oleclumab will be provided with either single-panel labels or multi-language booklet labels. The investigator's emergency contact details will not be on the label, but can be found in the informed consent and the 'Patient Emergency Card'. For emergency purposes, the patient must be in possession of the emergency contact details at all times.	Study drug will be provided in vials. Each vial will be labelled in accordance with GMP Annex 13 and per country regulatory requirement. Labels will be prepared in accordance with GMP and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language, as required. Durvalumab will be provided with either single-panel labels or multi-language booklet labels. The investigator's emergency contact details will not be on the label, but can be found in the informed consent and the 'Patient Emergency Card'. For emergency purposes, the patient must be in possession of the emergency contact details at all times.
Provider	AstraZeneca. Commercially available 0.9% (w/v) saline IV bags will be supplied by each site.	AstraZeneca. Commercially available 0.9% (w/v) saline or 5% (w/v) dextrose IV bags will be supplied by each site.

GMP Good Manufacturing Practice; IV intravenous(ly); Q2W every 2 weeks; Q4W every 4 weeks; w/v weight/volume

6.2 Preparation/handling/storage/accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study drugs received and any discrepancies are reported and resolved before use of the study drug.

Only patients enrolled in the study may receive study drugs and only authorised site staff may supply or administer study drugs. All study drugs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorised site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study drugs accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study drug are provided in the Pharmacy Manual.

6.2.1 Durvalumab preparation and handling

Durvalumab will be supplied by AstraZeneca as a 500-mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine hydrochloride, 275 mM trehalose dihydrate, and 0.02% (weight/volume [w/v]) polysorbate 80; it has a pH of 6.0 and a density of 1.054 g/mL. The nominal fill volume is 10.0 mL.

Study drug vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. The vials should be kept in the original packaging until use to prevent prolonged light exposure.

The dose of durvalumab for administration must be prepared by the investigator's or site's designated study drug manager using aseptic technique. Total time from needle puncture of the durvalumab vial to the start of administration should not exceed 4 hours at room temperature or 24 hours at 2°C to 8°C (36°F to 46°F). If the final product is stored at both refrigerated and ambient temperatures, the total time should not exceed 24 hours.

A dose of 1500 mg (for patients >30 kg body weight) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab concentration ranging from 1 to 15 mg/mL and delivered through an IV-administration set with a 0.2-µm or 0.22-µm filter. Add 30.0 mL (i.e., 1500 mg) of durvalumab to an appropriately sized IV bag such that the final concentration is within 1 to 15 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

If a patient's body weight falls ≤30 kg during the study, (s)he will be withdrawn from the study treatment unless (s)he derives some clinical benefit according to the treating physician. In this case, and following agreement between the treating physician and the Sponsor, the patient may continue treatment at a body-weight adapted dose of 20 mg/kg actual body weight.

Weight-based dosing at 20 mg/kg (for patients ≤30 kg) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab concentration

ranging from 1 to 15 mg/mL, and delivered through an IV administration set with a 0.2-µm or 0.22-µm filter. An example of a weight-based dose calculation is shown in Section 6.2.1.1.

Standard infusion time is one hour (±15 minutes), however if there are interruptions during infusion, the total allowed infusion time should not exceed 8 hours at room temperature.

If either preparation time or infusion time exceeds the time limits a new dose must be prepared from new vials. Durvalumab does not contain preservatives, and any unused portion must be discarded.

Do not co-administer other drugs through the same infusion line.

The IV line will be flushed with a volume of IV diluent equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered.

Durvalumab should be administered at least 15 minutes after the end of the oleclumab infusion, after the first cycle, as long as there are no acute infusion reactions to oleclumab. Patients will be monitored before, during, and after the first durvalumab infusion with assessment of vital signs at the times specified in the SoA (Table 1) and Section 8.2.3 of the core protocol. If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be at the investigator's discretion (suggested 30 minutes after each durvalumab infusion). For management of patients who experience an infusion reaction, please refer to the toxicity and management guidelines for infusion-related reactions at the following location: https://tmg.azirae.com.

Durvalumab (1500 mg) will be administered via IV infusion Q4W ± 2 days. Treatment with durvalumab will commence on Day 1 following confirmation of eligibility and will continue on a Q4W schedule until disease progression is confirmed.

6.2.1.1 Durvalumab weight-based calculation

If a patient's body weight falls ≤30 kg during the study, (s)he will be withdrawn from the study treatment unless (s)he derives some clinical benefit according to the treating physician. In this case, and following agreement between the treating physician and the Sponsor, the patient may continue treatment at a body-weight adapted dose of 20 mg/kg of durvalumab Q4W until the weight improves to >30 kg, at which point the patient should start receiving the fixed dosing of durvalumab 1500 mg Q4W:

1 Cohort dose: X mg/kg
2 Patient weight: Y kg
3 Dose for patient: XY mg = X (mg/kg) × Y (kg)
4 Dose to be added into infusion bag:

Dose (mL) = XY mg/50 (mg/mL) where 50 mg/mL is durvalumab nominal concentration. The corresponding volume of durvalumab should be rounded to the nearest tenth mL (0.1 mL). Dose adjustments for each cycle are only needed for greater than 10% change in weight.

5 The number of vials required for dose preparation is the next greatest whole number of vials from the following formula:
Number of vials = Dose (mL) / 10.0 (mL/vial)

Example:

1 Cohort dose: 20 mg/kg
   (a) Patient weight: 30 kg
   (b) Dose for patient: 600 mg = 20 (mg/kg) × 30 (kg)
   (c) Dose to be added into infusion bag:
   (d) Dose (mL) = 600 mg / 50 (mg/mL) = 12.0 mL
   (e) The number of vials required for dose preparation:
   Number of vials = 12.0 (mL) / 10.0 (mL/vial) = 2 vials

6.2.2 Oleclumab preparation and handling

Oleclumab will be supplied by AstraZeneca as a 500-mg vial solution for infusion after dilution. The solution contains 50 mg/mL oleclumab in 25 mM histidine/histidine hydrochloride, 240 mM sucrose, 0.03% (w/v) polysorbate 80; it has a pH of 6.0 and density of 1.05 g/mL. The nominal fill volume is 10.0 mL. Study drug vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Drug product should be kept in original secondary packaging to avoid prolonged exposure to light.

Oleclumab IV bag preparation and administration

No incompatibilities between oleclumab and polyvinyl chloride or polyolefin IV bags have been observed.

The dose of oleclumab for administration must be prepared by the investigator's or site's designated study drug manager using aseptic technique. Total time from needle puncture of the oleclumab vial to the start of administration should not exceed:

- 24 hours at 2°C to 8°C (36°F to 46°F)
- 4 hours at room temperature.

If the final product is stored at both refrigerated and ambient temperatures, the total time should not exceed 24 hours.

The dose of 3000 mg oleclumab (for patients >30 kg) will be administered using an IV bag containing 0.9% (w/v) saline, with a final in-bag oleclumab concentration ranging from 1.5 to 30 mg/mL, and delivered through an IV administration set with a 0.2 µm or 0.22 µm filter. Add 60.0 mL (ie, 3000 mg) of oleclumab to the IV bag. The IV bag size should be selected such that the final concentration is within 1.5 to 30 mg/mL. Mix the bag gently to ensure homogeneity of the dose in the bag.

If patient weight falls to ≤30 kg during the study, oleclumab should be withheld until the body weight increases to >30 kg. If treatment is withheld for more than 28 days and the patient's weight has not increased to >30 kg, the patient should permanently discontinue study treatment.

Standard infusion time is one hour (+15 minutes), however if there are interruptions during infusion, the total allowed infusion time should not exceed 4 hours at room temperature.

Do not co-administer other drugs through the same infusion line.

The IV line will be flushed with a volume of IV diluent equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered.

If either preparation time or infusion time exceeds the time limits a new dose must be prepared from new vials. Oleclumab does not contain preservatives, and any unused portion must be discarded.

Oleclumab should be administered before the patient receives their first durvalumab infusion. Patients will be monitored within 30 minutes before, every 30 minutes during, and within 30 minutes after the first oleclumab infusion with assessment of vital signs, as described in the SoA (Table 1) and Section 8.2.3 of the core protocol. Oleclumab infusion should be completed at least 30 minutes before the patient receives their first durvalumab infusion. If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be shortened at the investigator's discretion to at least 15 minutes after the end of the oleclumab infusion.

For management of patients who experience an infusion reaction, please refer to the toxicity and management guidelines for infusion-related reactions at the following location: https://tmg.azirae.com.

Oleclumab (3000 mg) will be administered via IV infusion Q2W ±2 days for 2 cycles and then Q4W ±2 days thereafter. Treatment with oleclumab will commence on Day 1 following confirmation of eligibility and will continue until disease progression is confirmed.

6.2.3 Study drug administration

It is important to follow the assessment schedule as closely as possible.

Patients should continue to receive study treatment (ie, durvalumab in combination with oleclumab) until objective radiological disease progression as per Response Evaluation Criteria in Solid Tumours (RECIST 1.1), as long as, in the investigator's opinion, they are benefiting from treatment and they do not meet any other discontinuation criteria. Disease progression should be confirmed by a subsequent scan (no earlier than 4 weeks later) in the absence of clinically significant deterioration as assessed by the investigator. All patients who have objective progression of disease will enter follow-up.

6.2.4 Storage

All study drugs should be kept in a secure place under appropriate storage conditions.

Durvalumab and oleclumab are to be stored at the study centre in a secured facility with limited access and controlled temperature (2ºC to 8ºC). The temperature should be monitored on a daily basis and documented in the temperature monitoring log according to the study drug handling instructions.

The study drug must be kept in the original outer container and under conditions specified on the labels.

In the following cases, the centre staff should not use affected study drug and should immediately contact AstraZeneca representative for further guidance:

- Temperature excursion upon receipt or during storage at the study site
- Damaged kit upon receipt
- Damaged vial/bottle

Damaged study drug should be documented according to the instructions provided by AstraZeneca representative. Storage conditions stated in the Investigator's Brochure, or the study drug Handling Instructions document, may be superseded by the label storage.

6.2.5 Accountability

The study drugs provided for this study should be used only as directed in the study protocol.

The study site staff will account for all study drugs received at the centre, for unused study drugs, and for appropriate destruction (according to local procedures). Certificates of delivery, destruction, and/or return should be signed.

The administration of all medications (including study drug) and details of treatment with study drug should be recorded in the appropriate sections of the electronic Case Report Form (eCRF).

6.3 Measures to minimise bias: randomisation and blinding

This is an open-label study.

Recruitment to the biomarker-matched cohorts will be based upon a predefined schema (described in the Pathology and Genomic Testing Manual) for patient allocation which takes account of biomarker prevalence estimates and the platform of evidence for each study treatment.

Recruitment into the biomarker non-matched arms will be conducted in a sequential manner.

If a patient withdraws from participation in the study, then his/her enrolment code cannot be reused. Withdrawn patients will not be replaced.

6.4 Treatment compliance

The administration of all study drugs should be recorded in the appropriate sections of the eCRF. Durvalumab and oleclumab will be administered on site. Treatment compliance will be assured by reconciliation of site drug accountability logs.

Any change from the dosing schedule, dose interruptions, or dose discontinuations should be recorded in the eCRF. Note: Dose reductions are not allowed for oleclumab. Dose reductions are not allowed for durvalumab (see Section 6.6).

The Study Drug Storage Manager is responsible for managing the study drug from receipt by the study site until the destruction or return of all unused study drug.

Use of study treatment in doses in excess of that specified in the protocol is considered to be an overdose. Refer to Section 8.4.3 for procedures in case of overdose.

6.5 Concomitant therapy

Any medication or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the patient is receiving at the time of enrolment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Prohibited concomitant medications are described in Table 3. Please refer to Section 8.4.5 for guidance on management of study drug-related toxicities.

The use of concomitant medications must be recorded in the eCRF.

Table 3 Prohibited medications

Prohibited medication/class of drug:	
Unless stated otherwise, these medications are prohibited from the time that patients enter the main screening period until the last dose of study treatment. The pre-screen may be done whilst on prior therapy.	
Any investigational anticancer therapy other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment
Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment. (Note: concurrent use of hormones for non-cancer-related conditions [eg, insulin for diabetes and hormone replacement therapy] is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable [eg, by local surgery or radiotherapy]). Patients may receive treatment with bisphosphonates or RANKL inhibitors for the treatment of bone metastases.
Immunosuppressive medications, including, but not limited to: systemic corticosteroids at doses exceeding 10 mg/day of prednisone or its equivalent, methotrexate, azathioprine, and tumour necrosis factor-α blockers	Should not be given concomitantly, or used for premedication prior to the infusions. The following are allowed exceptions: • Use of immunosuppressive medications for the management of study drug-related AEs • Short-term premedication for patients receiving combinations where the prescribing information for the agent requires the use of steroids for documented hypersensitivity reactions • Use in patients with contrast allergies • In addition, use of inhaled, topical, and intranasal corticosteroids is permitted. A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of non-immunotherapy related events experienced by the patient (eg, chronic obstructive pulmonary disease, radiation, nausea, etc).
Live attenuated vaccines	Prohibited from the time that patients enter the main screening period until 180 days after the last dose of study treatment.
Epidermal growth factor receptor (EGFR) Tyrosine kinase inhibitors (TKIs)	Should not be given concomitantly. Should be used with caution in the 90 days post last dose of durvalumab. Increased incidences of pneumonitis (with third generation EGFR TKIs) and increased incidence of transaminase increases (with 1st generation EGFR TKIs) have been reported when durvalumab has been given concomitantly
Herbal and natural remedies which may have immune-modulating effects	Should not be given concomitantly unless agreed by the sponsor

AE adverse event

The use of herbal preparations/medications should be discouraged throughout the study. These herbal medications include, but are not limited to: St. John's Wort, kava, ephedra (ma

huang), gingko biloba, dehydroepiandrosterone, yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 7 days prior to first dose of study drug (3 weeks for St John's Wort). Use of these products, as well as use of all vitamins, nutritional supplements and all prescribed concomitant medications, must be recorded in the eCRF.

Other concomitant treatment

Medication other than that described above, which is considered necessary for the patient's safety and wellbeing, may be given at the discretion of the investigator and recorded in the appropriate sections of the eCRF.

6.5.1 Rescue and supportive medication

The study site will supply rescue medication and this will be procured locally. The sponsor will supply only if required by local regulations.

The use of rescue medications is allowable at any time during the study. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

Supportive medication, described in Table 4, may be given at the discretion of the investigator and recorded in the appropriate section of the eCRF.

Table 4 Supportive medication

Supportive medication/class of drug:	Usage:
Concomitant medications or treatments (eg, acetaminophen or diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care, except for those medications identified as "prohibited," as listed above	To be administered as prescribed by the investigator
Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy to non-target lesions, etc])	Should be used, when necessary, for all patients
Inactivated viruses, such as those in the influenza vaccine	Permitted

6.6 Dose modification and discontinuation

For patients who weigh >30 kg, the doses of durvalumab and oleclumab cannot be modified. If a patient's body weight falls ≤30 kg during the study:

- Durvalumab: (s)he will be withdrawn from the study treatment unless (s)he derives some clinical benefit according to the treating physician. In this case, and following agreement between the treating physician and the Sponsor, the patient may continue treatment at a body-weight adapted dose of 20 mg/kg actual body weight.
- Oleclumab: oleclumab will be withheld until the body weight increases to above 30 kg. If the delay is more than 28 days, the patient will be withdrawn from oleclumab.

Durvalumab and oleclumab dosing can be temporarily interrupted in the event of treatment-related toxicity. All toxicities will be graded according to Common Toxicity Criteria for Adverse Events (CTCAE) version 4.03. Note: Dose reductions are not allowed for oleclumab. Dose reductions are not allowed for durvalumab. Please refer to Section 8.4.5.1 and to the toxicity management guidelines for durvalumab at the following location: URL: https://tmg.azirae.com.

Dose interruptions, and initiation of supportive care, are allowed as deemed appropriate by the treating physician. If Day 1 treatment with durvalumab or oleclumab is interrupted, then both study medications will be delayed until the combination can be resumed. The maximum interruption or cycle delay that is permitted is 28 continuous days. Any patient requiring a toxicity related dose delay of more than 28 days from the intended day of the next scheduled dose must be discontinued from the study unless there is approval from the Study Physician for the patient to continue.

6.7 Treatment after the end of the study

Patients are permitted to either receive standard of care therapy, or to continue to receive study treatment following the end of the study if, in the opinion of the investigator, they are continuing to receive benefit from treatment. After discontinuation of study treatment, the investigator will be at liberty to define further most appropriate anti-cancer treatment. Subsequent anti-cancer treatment is expected to be initiated following the cancer recurrence or development of a new cancer. Information on subsequent anti-cancer therapies should be recorded on the clinical database.

7. DISCONTINUATION OF TREATMENT AND PATIENT WITHDRAWAL

Please refer to Section 7 in the core protocol.

Guidance on re-allocation to a second treatment cohort is provided in Section 7.4 of the core protocol. See also criteria for stopping study drugs in Sections 7.1 and 8.4.5 of the core protocol.

Study procedures and their timing for patients re-allocated to a second study treatment are summarised in the re-allocation SoA (Table 5). Note: From implementation of protocol v10.0,

optional treatment re-allocation of patients to a second treatment cohort is no longer applicable.

Table 5 Schedule of Activities for patients re-allocated to second on-treatment period (Module 5)

	C1 28 days Weeks 1-4		C2 28 days Weeks 5-8		C3 28 days Weeks 9-12	C4 28 days Weeks 13-16	C5 – etc All cycles 28 days	Study drug disc. (28 days after study drug disc.)	Safety follow-up (90 days after study drug disc.)	Survival follow up	Notes
Week	**1**	**3**	**5**	**7**	**9**	**13**	**17, 21, 25, 29 etc**				
Cycle day	**1**	**15**	**1**	**15**	**1**	**1**	**1**				
Window (days)	**0[a]**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±7**	**±7**	**±7**	
Study procedures											
Informed consent	X										Section 5.2.1 (core protocol). Patient must consent to new treatment. Will be performed within 28 days before dosing.
Eligibility criteria for re-allocation[b]	X										Patients must meet eligibility criteria in the core CSP (see Table 1) and in this module
Physical examination	X	X	X	X	X	X	X	X			Section 8.2.2 (core protocol)
Vital signs	X	X	X	X	X	X	X	X			Section 8.2.3 (core protocol)
ECG	X	As clinically indicated									Section 8.2.4 (core protocol)
Concomitant medications	X	X	X	X	X	X	X	X			Section 6.5
Laboratory assessments											
Clinical chemistry	X	X	X	X	X	X	X	X			Section 8.2.1 (core protocol). If screening laboratory assessments are performed within 3 days prior to Day 1 they do not need to be repeated at Day 1
Haematology	X	X	X	X	X	X	X	X			
APTT and INR		As clinically indicated									
TSH, free T_3, and free T_4	X	X	X	X	X	X	X	X			Section 8.2.1 (core protocol)
Urinalysis		As clinically indicated									Section 8.2.1 (core protocol)
Pregnancy test	X		X		X	X	X	X			Section 8.2.1.2 (core protocol)

	C1 28 days Weeks 1-4		C2 28 days Weeks 5-8		C3 28 days Weeks 9-12	C4 28 days Weeks 13-16	C5 – etc All cycles 28 days	Study drug disc. (28 days after study drug disc.)	Safety follow-up (90 days after study drug disc.)	Survival follow up	Notes
Week	**1**	**3**	**5**	**7**	**9**	**13**	**17, 21, 25, 29 etc**				
Cycle day	**1**	**15**	**1**	**15**	**1**	**1**	**1**				
Window (days)	**0[a]**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±7**	**±7**	**±7**	
AE/SAE assessment	X	X	X	X	X	X	X	X	X		Section 8.3 (core protocol)
Study drug administration											
Durvalumab	X		X		X	X	X				Section 6.2.1
Oleclumab	X	X	X	X	X	X	X				Section 6.2.2
Drug accountability	X	X	X	X	X	X	X	X			Section 6.2.5
Other assessments											
Subsequent cancer therapy									X	X	These assessments are repeated here from Table 1. Patients will be followed for survival from the original treatment cohort. These are not additional assessments for re-allocation, they are only repeated here for completeness.
Survival status										X	

[a] Every effort should be made to minimise the time between allocation to treatment and starting treatment.
[b] Eligibility criteria in core CSP and in this module apply

Note, if main screening assessments have been performed within 3 days prior to C1D1, then assessments do not need to be performed on C1D1 pre-dose.
AE adverse event; APTT activated partial thromboplastin time; C cycle; ECG electrocardiogram; ECOG Eastern Cooperative Oncology Group; INR international normalised ratio; SAE serious adverse event; TSH thyroid-stimulating hormone; T_3 triiodothyronine; T_4 thyroxine; WHO World Health Organization.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in the SoA (Table 1). Study procedures and their timing for patients re-allocated to a second study treatment are summarised in the re-allocation SoA (Table 5).

8.1 Efficacy assessments

Please refer to the core protocol.

8.2 Safety assessments

8.2.1 Clinical safety laboratory assessments

Please refer to core protocol.

8.2.1.1 Coagulation

Please refer to core protocol.

8.2.1.2 Other safety assessments

Please refer to core protocol.

8.2.1.3 Pneumonitis (interstitial lung disease) investigation

The following assessments, and additional assessments if required, will be performed to enhance the investigation and diagnosis of potential cases of pneumonitis. The results of the assessment will be collected.

- Physical examination; Signs and symptoms (cough, shortness of breath and pyrexia, etc) including auscultation for lung field will be assessed.
- SpO_2; Saturation of peripheral oxygen (SpO_2)
- Other items; When pneumonitis (interstitial lung disease [ILD]) is suspected during study treatment, the following markers should be measured where possible:
  - ILD markers (KL-6, SP-D) and β-D-glucan
  - Tumour markers: Particular tumour markers which are related to disease progression.

8.2.2 Physical examinations

Please refer to core protocol.

8.2.3 Vital signs

Please refer to core protocol.

8.2.4 Electrocardiograms

Please refer to core protocol.

8.2.5 Performance status

Please refer to core protocol

8.3 Collection of adverse events

Please refer to the core protocol.

8.4 Safety reporting and medical management

8.4.1 Reporting of serious adverse events

Please refer to the core protocol.

8.4.2 Pregnancy

Please refer to the core protocol.

8.4.3 Overdose

Please refer to the core protocol.

8.4.4 Medication error

Please refer to the core protocol. Module 5 (HUDSON)

8.4.5 Management of study drug-related toxicities

Given the differing mechanisms of action of durvalumab and oleclumab, the potential for potentiation of toxicities is thought to be limited. Immune-mediated toxicities may, on theoretical grounds, be potentiated in the combination arm and particular attention should be paid to these.

In the event of toxicity in this combination arm of the study which cannot be managed by supportive measures alone, stopping one or both medications should be an investigator decision based on the available information and, if necessary, following discussion with the sponsor.

The following general guidance should be followed for management of toxicities:

- Treat each of the toxicities with maximum supportive care (including withholding the agent suspected of causing the toxicity if required).
- If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of the assigned study drug along with appropriate continuing supportive care. In the event of toxicity that cannot be managed by following the toxicity management guidelines for oleclumab and durvalumab, consider stopping treatment with oleclumab.

8.4.5.1 Management of toxicity related to durvalumab and oleclumab combination therapy

Please refer to the toxicity management guidelines for durvalumab at the following location: URL: https://tmg.azirae.com.

8.4.6 Adverse events of special interest

Adverse events of special interest (AESIs) are events of scientific and medical interest specific to understanding of the study drug profile and may require close monitoring. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing analysis of these events in order to characterise and understand them in association with the use of the study drug.

The AESIs for durvalumab are summarised in core protocol Section 8.3.12.

The AESIs for oleclumab are summarised below.

Infusion-related reactions (IRRs)

Intravenous administration of mAbs can cause an acute reaction called IRR. Acute allergic reactions may also occur during the infusion of investigational product. Manifestations of IRR and acute allergic reactions are similar and they are managed the same way. IRRs predominantly occur at the first exposure to drug, and are uncommon at subsequent exposures. The sponsor requests that study sites include the signs/symptoms that occur during or after an infusion of oleclumab. Guidelines for management of subjects with hypersensitivity (including anaphylactic reaction) and IRRs are provided in the Toxicity Management Guidelines.

Cardiac chest pain, transient ischemic attack, and thromboembolism

AEs of cardiac chest pain, transient ischemic attack, and thromboembolic events are of special interest due to oleclumab potential risks of arterial calcifications, arterial ischemic disorder, and thrombosis. Because of this potential risk, subjects with a prior history of myocardial infarction, stroke or transient ischemic attack in the past 3 months are not eligible (see exclusion criteria). These events require urgent medical management, which should be performed according to consensus guidelines developed by the American Heart Association or appropriate local standards of care.

Oedema

Oedema (eg, pulmonary, peripheral, or pleural effusion) is regarded as AESI due to oleclumab potential risks of increased microvascular permeability. For subjects who develop ≥Grade 3 oedema, doses should be omitted as described in the toxicity management guidelines, and therapy may be discontinued at the discretion of the investigator.

Immune complex disease

The immune system can respond to foreign protein, even to humanized mAb by producing human anti-human antibodies, which may result in formation of immune complexes and their deposition in blood vessels, joints, and glomeruli causing symptomatic disease (eg, vasculitis, glomerulonephritis, arthritis, serum sickness). Subjects will be monitored clinically. Subjects who experience an AE suspected to be immune-complex related will discontinue treatment. Immune-complex disease will be managed in accordance with standard of care.

8.5 Pharmacokinetics

Please refer to the core protocol.

8.6 Pharmacodynamics

Pharmacodynamic parameters will be evaluated in this study (see Section 8.6 of the core protocol).

8.7 Genetics

Please refer to the core protocol.

8.8 Biomarkers

Please refer to the core protocol. CD73-specific biomarker status will be obtained from samples collected as described in the core protocol.

8.9 Medical Resource Utilisation and Health Economics

Health Economics/Medical Resource Utilisation and Health Economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

Please refer to the core protocol.

10. REFERENCES

Antonioli et al 2013
Antonioli L, Blandizzi C, Pacher P, Hasko G. Immunity, inflammation and cancer: a leading role for adenosine. Nat Rev Cancer. 2013;13(12):842-57.

Garassino et al 2017
Garassino M, Vansteenkiste J, Joo-Hang K, Hervé L, Mazières J, Powderly J, et al. Durvalumab in ≥3rd-Line Locally Advanced or Metastatic, EGFR/ALK Wild-Type NSCLC: Results from the Phase 2 ATLANTIC Study. J Thor Onc 2017;12:S10-S11.

Inoue et al 2017
Inoue Y, Yoshimura K, Kurabe N, Kahyo T, Kawase A, Tanahashi M et al. Prognostic impact of CD73 and A2A adenosine receptor expression in non-small-cell lung cancer. Oncotarget. 2017;8(5):8738-51.

Jin et al 2010
Jin D, Fan J, Wang L, Thompson LF, Liu A, Daniel BJ et al. CD73 on tumor cells impairs antitumor T-cell responses: a novel mechanism of tumor-induced immune suppression. Cancer Res. 2010;70(6):2245-55.

Narwal et al 2013
Narwal R, Roskos LK, Robbie GJ. Population Pharmacokinetics of Sifalimumab, an Investigational Anti-Interferonalpha Monoclonal Antibody, in Systemic Lupus Erythematosus. Clin Pharmacokinet 2013;52:1017–27.

Ng et al 2006
Ng CM, Lum BL, Gimenez V, Kelsey S, Allison D. Rationale for fixed dosing of pertuzumab in cancer patients based on population pharmacokinetic analysis. Pharm Res 2006;23(6):1275–84.

Sadej et al 2006
Sadej R, Spychala J, Skladanowski AC. Ecto-5'-nucleotidase (eN, CD73) is coexpressed with metastasis promoting antigens in human melanoma cells. Nucleosides Nucleotides Nucleic Acids. 2006;25(9-11):1119-23.

Spychala 2000
Spychala J. Tumor-promoting functions of adenosine. Pharmacol Ther. 2000;87(2-3):161-73.

Spychala et al 2004
Spychala J, Lazarowski E, Ostapkowicz A, Ayscue LH, Jin A, Mitchell BS. Role of estrogen receptor in the regulation of ecto-5'-nucleotidase and adenosine in breast cancer. Clin Cancer Res. 2004;10(2):708-17.

Stagg et al 2010
Stagg J, Divisekera U, McLaughlin N, Sharkey J, Pommey S, Denoyer D et al. Anti-CD73 antibody therapy inhibits breast tumor growth and metastasis. Proc Natl Acad Sci U S A. 2010;107(4):1547-52.

Wang et al 2008
Wang L, Zhou X, Zhou T, Ma D, Chen S, Zhi X et al. Ecto-5'-nucleotidase promotes invasion, migration and adhesion of human breast cancer cells. J Cancer Res Clin Oncol. 2008;134(3):365-72.

Wang et al 2009
Wang DD, Zhang S, Zhao H, Men AY, Parivar K. Fixed dosing versus body size based dosing of monoclonal antibodies in adult clinical trials. J Clin Pharmacol 2009;49(9):1012–24.

Young et al 2016
Young A, Ngiow SF, Barkauskas DS, Sult E, Hay C, Blake SJ et al. Co-inhibition of CD73 and A2AR Adenosine Signaling Improves Anti-tumor Immune Responses. Cancer Cell. 2016;30(3):391-403.

Zhang 2010
Zhang B. CD73: a novel target for cancer immunotherapy. Cancer Res. 2010;70:6407-11.

Zhang et al 2012
Zhang S, Shi R, Li C, Parivar K, Wang DD. Fixed dosing versus body size-based dosing of therapeutic peptides and proteins in adults. J Clin Pharmacol 2012;52(1):18–28.

Zhi et al 2007
Zhi X, Chen S, Zhou P, Shao Z, Wang L, Ou Z et al. RNA interference of ecto-5'-nucleotidase (CD73) inhibits human breast cancer cell growth and invasion. Clin Exp Metastasis. 2007;24(6):439-48.

Zou et al 2016
Zou W, Wolchok JD, Chen L. PD-L1 (B7-H1) and PD-1 pathway blockade for cancer therapy: Mechanisms, response biomarkers, and combinations, Sci Trans Med. 2016; 8:328.

Clinical Study Protocol

Drug Substance	Umbrella study
Study Code	D6185C00001 (HUDSON)
Version	14.0
Date	09 October 2024

Appendix N

Module 6: Durvalumab plus trastuzumab deruxtecan (DS-8201a)

An Open-Label, Multi-Drug, Biomarker-Directed, Multi-Centre Phase II Umbrella Study in Patients with Non-Small Cell Lung Cancer, who Progressed on an Anti-PD-1/PD-L1 Containing Therapy (HUDSON)

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

Regulatory Agency Identification Numbers:

EudraCT number: 2017-002208-28

EU CT number: 2023-509004-15-00

IND number: 138050

VERSION HISTORY

Version 14.0, 09 October 2024
Key amendments and rationale for changes: The version number of this module has been revised in line with the other modules in the HUDSON study; however, no changes have been made to this module.

Version 13.0, 14 December 2023
Key amendments and rationale for changes: **Front page:** EU CT number has been added in line with the core CSP. **Section 6.1.1, study drugs:** Text regarding 'Packaging and Labelling' updated to remove the information that labels will fulfil GMP Annex 13 requirements for labelling, as this Annex has been replaced. **Section 6.2.3, study drug administration:** The note regarding steroid prophylaxis was removed for consistency with the trastuzumab deruxtecan IB.

Version 12.0, 01 March 2023
Key amendments and rationale for changes: **Table 1, schedule of activities:** • Addition of a footnote to clarify the windows allowed for the administration of the study drugs. **Section 4.1, overall design, Section 6.2.1, durvalumab preparation and handling, Table 4, study drugs:** The windows for study drugs administration were clarified. **Section 4.3.1, justification for durvalumab dose:** Added a cross-reference to the durvalumab IB for updates on data from ongoing studies. **Section 6.2, preparation/handling/storage/accountability:** Added a reference to the Pharmacy Manual.

Section 6.2.3, study drug administration: Text regarding prophylactic antiemetic agents was updated in line the trastuzumab deruxtecan IB Edition 9.

Table 5, prohibited medications: Updated in line with the changes in Section 6.2.3.

Table 6, supportive medication: Updated in line with the changes in Section 6.2.3.

Table 7, toxicity management guidelines for trastuzumab deruxtecan: Text regarding ILD/pneumonitis events was updated in line the trastuzumab deruxtecan IB Edition 9.

Version 11.0, 16 August 2022

Key amendments and rationale for changes:

Table 1, schedule of activities – treatment intervention period (Module 6):

- Footnote m (describing collection of ADA samples beyond the 30-day safety follow-up) is removed as additional sample collection is not required given the low immunogenicity risk for trastuzumab deruxtecan and to align with the impending Project Specific Safety Requirements update. Remaining footnote identifiers are updated accordingly.
- Removal of CCI sample collection on Day 8 (Cycles 1 and 2), text related to collection for subsequent cycles deleted and footnote added to clarify timing of sample collection. This change is made to align with other AstraZeneca projects.
- Addition of footnote to clarify an on-treatment biopsy is not required if a fresh tumour sample is not collected at pre-screening. Analysis requires a baseline result for comparison (ie, from the pre-screening sample).

Version 10.0, 12 April 2022

Key amendments and rationale for changes:

Table 1, schedule of activities:

- Footnotes c, d and f updated to clarify timings of assessments before, during and after each study treatment infusion. Related text in Section 8.2.3, vital signs also clarified.
- Addition of footnote q to clarify activities for patients continuing on study treatment after the data cut-off for the module clinical study report.
- Update to footnote m to clarify collection of additional ADA samples relates to trastuzumab deruxtecan-positive ADA.

- Troponin collection frequency reduced to align with the trastuzumab deruxtecan Project Specific Safety Requirements (v6); related text in footnote h, and related text in Section 8.2.1, clinical safety laboratory assessments and Section 8.4.5.4, LVEF management guidance, also aligned accordingly.

Figure 1, study design: Footnote added to clarify survival follow-up of screen failures is no longer required from implementation of protocol v10.0.

Section 1.3.1, safety run-in: Text describing definition of a DLT for haematological toxicities and hepatic organ toxicities updated to align with trastuzumab deruxtecan PSSR v6.0.

Section 2.2, background: Reference to approval of durvalumab for the treatment of urothelial carcinoma in the US removed due to voluntary withdrawal of this indication in this country. Text also added to clarify the weight-based regimen (10 mg/kg every 2 weeks) is approved for urothelial carcinoma.

Section 2.2.1.2, durvalumab data: Number of patients treated with durvalumab updated to align with durvalumab IB Edition 17.

Section 2.2.2, background for trastuzumab deruxtecan; Section 2.3.1 trastuzumab deruxtecan benefit/risk: Text updated to align with trastuzumab deruxtecan IB Edition 8. Identified risks also updated in Section 2.3.1 to align with trastuzumab deruxtecan PSSR v6.0.

Section 5.1, inclusion criteria: New inclusion criteria for reproduction and contraception requirements (N-5, N-6 and N-7) added to align with trastuzumab deruxtecan PSSR v6.0.

Section 5.2, exclusion criteria (module 6-specific): Exclusion criteria N-7 and N-9 language updated, and new exclusion criterion N-14 included (previous severe toxicity judged by the investigator as clinically significant, observed during previous exposure to any of the study medications), to align with trastuzumab deruxtecan PSSR v6.0.

Section 5.3.1, restrictions applicable to durvalumab; Table 5, supportive medication: Text added to provide guidance for the use and timing of authorised and approved COVID-19 vaccines, to align with the COVID-19 vaccination guidance letter (dated 24 February 2021) provided to sites. Text for live attenuated vaccines also amended for clarification.

Sections 8.2.1.3, pneumonitis (interstitial lung disease) investigation, Section 8.4.5.3, ILD management guidance: Text related to ILD adjudication committee revised to align with trastuzumab deruxtecan PSSR v6.0.

Section 8.6, pharmacodynamics: Text updated to clarify pharmacodynamic parameters will be evaluated in the study and a cross reference to Section 8.6 of the core protocol added.

In addition, minor typographical errors have been corrected throughout where applicable.

Version 9.0, 14 May 2021

Key amendments and rationale for changes:

The version number of this module has been revised in line with the other modules in the HUDSON study; however, no changes have been made to this module.

Version 8.0, 11 September 2020

Key amendments and rationale for changes:

Removal of web link to the durvalumab toxicity management guidelines as this website has been decommissioned. The toxicity management guidelines will instead be provided to sites: Section 6.2.1, Section 6.6, and Section 8.4.5.1.

Table 1 Schedule of Activities:

- Footnote c – update to clarify the vital signs assessments to be taken around the time of the durvalumab infusion.
- Footnote d – update to clarify the cycles at which ECHO/MUGA need to be conducted (and Section 8.2.1.2).
- Footnote f – SpO_2 split into its own footnote for clarity.
- Footnote h - update to clarify the timings of the troponin sampling at treatment visits.
- Update to the table: Number of samples for CCI assessment reduced after Week 24 to once every 3 cycles rather than once every cycle. To reduce the sampling burden on patients.
- Update that pulmonary HRCT should be conducted, or MRI if agreed by the Sponsor (and Section 8.2.1.2).

Figure 1: Footnote added that additional screening assessments for Module 6 are shown in Table 1.

Section 1.3.1 (Safety run-in): change to allow a revised dose of trastuzumab deruxtecan to be proposed after the safety run-in.

Section 2.2.2.2 (Trastuzumab deruxtecan data): Updates to align with trastuzumab deruxtecan IB Edition 7.

Section 2.3.1 (Trastuzumab deruxtecan benefit/risk): Updates to reflect the latest safety information in trastuzumab deruxtecan IB Edition 7.

Section 4.1 (Overall design) and Section 9 (Statistical considerations): Exploratory analyses of biomarker tests for HER2 expression added. The exploratory data will contribute to understanding of HER2 expression in NSCLC and inform the feasibility to align tests for HER2 expression across the trastuzumab deruxtecan clinical development programme.

Section 5.1 (Inclusion criteria):

- Inclusion criterion N-3 – change to washout for chloroquine/hydroxychloroquine to > 14 days. To correct an error. Also applies to Section 11.
- Inclusion criterion N-4 – added to specify washouts required for major surgery, radiation therapy, anticancer therapy, and antibody-based cancer therapy.

Section 5.2 (Exclusion criteria):

- Exclusion criterion N-2 – update to clarify that patients who require ongoing blood transfusions are to be excluded.
- Exclusion criterion N-7 – clarification that pulmonary involvement of inflammatory disorders should be documented or presumable.

Section 8.2.3 (Vital signs): update to clarify the vital signs assessments to be taken around the time of the durvalumab infusion.

Version 7.0, 21 May 2020
Key amendments and rationale for changes:

Updates to address COVID-19-specific safety concerns:

- **Table 1 Schedule of Assessments:**
  - addition of blood samples for plasma and serum exploratory or safety analyses (new row in table and footnote m) (also Section 8.8)
  - new footnote k for additional PK blood samples for patients who receive chloroquine or hydroxychloroquine.
- **Section 5.1 Inclusion criteria:** Addition of new inclusion criterion to ensure patients have an adequate washout of chloroquine/hydroxychloroquine of ≥ 14 days prior to starting treatment.
- **Section 8.3 Collection of adverse events:** Instruction that COVID-19 infections should be reported in the eCRF.
- **Table 3 Prohibited medications:** Addition of chloroquine and hydroxychloroquine.
- **Addition of Section 11:** Instructions related to COVID-19.

Other changes (not COVID-19-related)

Table 1 Schedule of Assessments:

- Removal of MRI as an alternative to HRCT (also Section 8.2.1.2).
- Footnote b: new footnote. Medical history should include history of tobacco use, e-cigarettes and vaping (also Section 5.3.2)
- Footnote c: Update to the timing of vital signs and SpO_2 assessments (also Sections 8.2.1.2 and 8.2.3).
- Footnote e: clarification that ophthalmologic assessments should be conducted as clinically indicated.
- Footnote g: Updated to state that if it is not possible to assess troponin T, then sites should assess troponin I (also Sections 8.2.1 and 8.4.5.4).
- Footnote n: Minimum requirements for pulmonary function tests added.

Section 1.3.1 Safety run-in: Updates to DLT criteria in line with the latest safety information.

Figure 2 (safety run-in flow chart): Updates to state that if patients have ≥ 2 DLTs, recruitment should be stopped. This change was made so that patients dosed in the safety run-in who do not experience DLTs may continue to receive study drug whilst deriving clinical benefit.

Section 2.2 Background: Update to the registered use and approvals for durvalumab.

Figure 3 (study flow diagram): This figure has been removed from all modules and a cross reference added to the same figure in the core protocol instead. Change made to limit the number of modules requiring updating during a protocol amendment whenever a new module is added.

Section 5.2 Exclusion criteria:

- Exclusion N-2 modified to allow partial thromboplastin time.
- Exclusion N-3 updated to make it a requirement that patients who have increased troponin but no symptoms of myocardial infarction have a cardiology consultation to rule out myocardial infarction.
- Exclusion N-5 modified to exclude all patients with a history of ILD, not just those who had ILD that required steroids.
- Exclusion N-6 deleted.
- Exclusion N-7 minor modifications.
- Exclusion N-8 deleted.

Section 5.3.2 Restrictions applicable to trastuzumab deruxtecan: Specification that tobacco, e-cigarettes and vaping are strongly discouraged but not prohibited.

Section 6.2.1 Durvalumab preparation and handling: Clarification that if the final product is stored at both refrigerated and ambient temperatures, the total time should not exceed 24 hours.

Section 6.2.2 Trastuzumab deruxtecan preparation and handling: Text added to clarify that the patient's weight at Screening (baseline) will be used to initially calculate the dose of trastuzumab deruxtecan. For subsequent cycles, if the patient's weight increases or decreases by ≥ 10%, the dose will be recalculated. Change made for consistency with the Pharmacy manual.

Section 6.2.3 Study drug administration: Addition of recommendation that patients receive prophylactic anti-emetics prior to administration of trastuzumab deruxtecan (also Table 6).

Section 6.4 Treatment compliance: Clarification that dose reductions are not permitted for durvalumab.

Section 8.2.1.3 Pneumonitis (interstitial lung disease investigation) and **Section 8.4.5.3 ILD management guidance**: Added that an ILD adjudication committee and charter are to be established.

Section 8.3 Collection of adverse events: Information on safety follow up for ILD. **Section 8.4.5.3 ILD management guidance:** Updates to the analysis of ILD events. Figure 4 (now Figure 3) updated. **Section 8.4.5.4 LVEF management guidance:** Sentence amended to remove reference to troponin testing at a central laboratory, as troponin is assessed locally. **Table 5 Toxicity management guidelines for trastuzumab deruxtecan:** Updated in line with the most recent safety information.

Version 6.0, 05 November 2019
Initial creation of Module 6

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

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1. PROTOCOL SUMMARY

1.1 Schedule of Activities (SoA)

The Schedule of Activities (SoA) for the on-treatment period for Module 6 is shown in Table 1 below. For the SoA for the pre-screening visit, please refer to the core protocol. The main screening assessments are also presented in the core protocol; however as there are additional main screening requirements in Module 6, a column showing these has also been added to Table 1 of the current document.

Note that for this module, treatment cycles are 3 weeks, not the 4 weeks used in other modules.

This module will conduct a safety run-in comprising approximately 6 patients for 2 cycles. A safety evaluation will be performed on those 6 patients before further patients can be recruited into the module. See Section 1.3.1 for further details.

Table 1 Schedule of Activities – Treatment intervention period (Module 6)

	Screening (time prior to starting trt)	**C1** 21 days Weeks 1-3			**C2** 21 days Weeks 4-6			**C3** 21 days Weeks 7-9	**C4** 21 days Weeks 10-12	**C5 – etc** All cycles 21 days	**Study drug disc.** (28 days after study drug disc.)	**Safety follow-up** (90 days after study drug disc.)	**Survival follow up**	**Notes**
Week	**≤4 wks**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**10**	**13, 16, 19, 22 etc**				
Cycle day	**≤28 d**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**1**	**1**				
Window (days)		**0**[a]	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±7**	**±7**	**±7**	
Informed consent: main screening														
Informed consent: study procedures	X													Section 5.2.1 (core protocol)
Consent for genetic sample and analysis (optional)	X													Section 8.7 and Appendix D (core protocol)
Study procedures[p]														
Eligibility criteria	X													Section 5.1 and 5.2 (core protocol)
Medical history, including tobacco use[b]	X													Sections 4.1.4 and 5.4 (core protocol)
Physical examination	X	X	X		X	X		X	X	X	X	X		Section 8.2.2 (core protocol)
Vital signs	X	X[c]	X	X	X[c]	X		X[c]	X	X	X	X		Section 8.2.3
ECG[q]	X	X			X			X	X	X	X			Section 8.2.4 (core protocol)
Echocardiogram/ MUGA (LVEF)[d]	A								X	X (C8D1 then every 4th cycle)	X			See Section 8.2.1.2 (this module)
Weight, ECOG performance status	X	X			X			X	X	X	X	X		Section 8.2.5 (core protocol)
Ophthalmologic examination[e]	A										X			See Section 8.2.1.2 (this module)

	Screening (time prior to starting trt)	**C1** 21 days Weeks 1-3			**C2** 21 days Weeks 4-6			**C3** 21 days Weeks 7-9	**C4** 21 days Weeks 10-12	**C5 – etc** All cycles 21 days	**Study drug disc.** (28 days after study drug disc.)	**Safety follow-up** (90 days after study drug disc.)	**Survival follow up**	**Notes**
Week	**≤4 wks**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**10**	**13, 16, 19, 22 etc**				
Cycle day	**≤28 d**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**1**	**1**				
Window (days)		**0**[a]	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±7**	**±7**	**±7**	
SpO_2[f]	A	X	X	X	X			X	X	X	X	X		See Section 8.2.1.2 (this module)
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X			Section 6.5
Laboratory assessments[p]														
Clinical chemistry	X	X	X	X	X	X	X	X	X	X	X	X		Section 8.2.1 (core protocol). If screening assessments are performed within 3 days prior to D1 they do not need to be repeated at D1
Haematology	X	X	X	X	X	X	X	X[g]	X[g]	X[g]	X	X		
APTT and INR	X		As clinically indicated											
TSH, free T_3, and free T_4	X	X	X		X	X		X	X	X	X			Section 8.2.1 (core protocol)
Troponin[h]	A										X			See Section 8.2 (this module)
Urinalysis	X		As clinically indicated											Section 8.2.1 (core protocol)
Hepatitis B and C and HIV	X													Sections 5.2 and 8.2.1.2 (core protocol)
Pregnancy test	X	X			X			X	X	X	X	X		Section 8.2.1.2 (core protocol)
AE/SAE assessment	X	X	X	X	X	X	X	X	X	X	X	X		Section 8.3 (core protocol)

	Screening (time prior to starting trt)	**C1** 21 days Weeks 1-3			**C2** 21 days Weeks 4-6			**C3** 21 days Weeks 7-9	**C4** 21 days Weeks 10-12	**C5 – etc** All cycles 21 days	**Study drug disc.** (28 days after study drug disc.)	**Safety follow-up** (90 days after study drug disc.)	**Survival follow up**	**Notes**
Week	**≤4 wks**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**10**	**13, 16, 19, 22 etc**				
Cycle day	**≤28 d**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**1**	**1**				
Window (days)		**0**[a]	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±7**	**±7**	**±7**	
Study drug administration[p,t]														
Durvalumab		X			X			X	X	X				Section 6.2.1
Trastuzumab deruxtecan		X			X			X	X	X				Section 6.2.2
Drug accountability		X			X			X	X	X	X			Section 6.2.5
Other assessments														
Blood for [redacted] assessments[r]	X[i]	X			X			X	X	X	X			Section 8.8 (core protocol)
Genetic sample (optional DNA for long-term storage/future use)	X[j]													Section 8.7 (core protocol)
Circulating soluble factors (plasma)		X	X		X				X		X			Section 8.8 (core protocol)
Whole blood for gene expression (PAXgene® RNA tubes)		X	X		X				X		X			Section 8.8 (core protocol)
PBMCs for flow cytometry (activation by PD-1 / CD8+)	X	X	X		X				X					Section 8.8 (core protocol)
TCR immuno-sequencing		X	X		X				X					Section 8.8 (core protocol)

	Screening (time prior to starting trt)	**C1** 21 days Weeks 1-3			**C2** 21 days Weeks 4-6			**C3** 21 days Weeks 7-9	**C4** 21 days Weeks 10-12	**C5 – etc** All cycles 21 days	**Study drug disc.** (28 days after study drug disc.)	**Safety follow-up** (90 days after study drug disc.)	**Survival follow up**	**Notes**
Week	**≤4 wks**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**10**	**13, 16, 19, 22 etc**				
Cycle day	**≤28 d**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**1**	**1**				
Window (days)		**0[a]**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±7**	**±7**	**±7**	
Blood sample for durvalumab and trastuzumab deruxtecan PK[k,l]		X			X				X		X			Section 8.5 (core protocol), and Section 11
Blood sample for ADA for durvalumab and trastuzumab deruxtecan (pre-dose except at safety follow up)		X			X					X (C5D1) then Q12W in first year, then Q24W in second year		X		Section 8.5.3 (core protocol)
Blood sample for plasma and serum exploratory clinical benefit or safety analyses[m]		X							X	X (C8D1 and every 4 cycles thereafter)				Section 8.8
Tumour evaluation (CT or MRI) (RECIST 1.1)	X		Every 6 weeks ± 1 week for the first 24 weeks relative to the date of first dose (Cycle 1 Day 1), then every 9 weeks ± 1 week thereafter, until objective disease progression as defined by RECIST 1.1 and confirmed with a subsequent scan (in the absence of clinically significant deterioration)											Section 8.1 (core protocol)
Pulmonary HRCT (or MRI if agreed by Sponsor)	A													See Section 8.2.1.2 (this module)
Pulmonary function test[n]	A													See Section 8.2.1.2 (this module)

	Screening (time prior to starting trt)	**C1** 21 days Weeks 1-3			**C2** 21 days Weeks 4-6			**C3** 21 days Weeks 7-9	**C4** 21 days Weeks 10-12	**C5 – etc** All cycles 21 days	**Study drug disc.** (28 days after study drug disc.)	**Safety follow-up** (90 days after study drug disc.)	**Survival follow up**	**Notes**
Week	**≤4 wks**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**10**	**13, 16, 19, 22 etc**				
Cycle day	**≤28 d**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**1**	**1**				
Window (days)		**0**[a]	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±7**	**±7**	**±7**	
Biopsy on-treatment (mandatory)[s]								X						Section 8.8 (core protocol). This should align with the first RECIST assessment.
Biopsy on disease progression											X			Section 8.8 (core protocol)
Subsequent cancer therapy												X	X	Section 8.1.3.1 (core protocol). Every 3 months
Survival status													X[o]	Section 8.1.3.1 (core protocol). Every 3 months

[a] Every effort should be made to minimise the time between allocation to treatment and starting treatment. Note, if main screening assessments have been performed within 3 days prior to C1D1, then assessments do not need to be performed on C1D1 pre-dose.

[b] Medical History: to include history, type and frequency of tobacco use, e-cigarette use, vaping (including dates)

[c] Vital signs: on C1D1, C2D1 and C3D1 vital signs to be assessed before and after infusion of trastuzumab deruxtecan, and around the infusion of durvalumab according to the instructions for the durvalumab infusion in Section 8.2.3.1 of the core protocol. At subsequent cycles from Cycle 4 onwards BP, pulse rate, and other vital signs should be measured and collected/recorded in the eCRF prior to the start of the trastuzumab deruxtecan infusion. Patients should be carefully monitored, and BP and other vital signs should be measured during and after trastuzumab deruxtecan and durvalumab infusions as per institution standard and as clinically indicated.

[d] ECHO or MUGA scan assessments (note: the same test must be used for the subject throughout the study) will be performed at Screening and before trastuzumab deruxtecaninfusion on C4D1 and then prior to the onset of every 4th cycle (± 7 days) (C8, C12 etc).

[e] Ophthalmologic assessments including visual acuity testing, slit lamp examination and fundoscopy will be performed at Screening, study drug discontinuation and as clinically indicated.

[f] SpO_2: to be performed before and after infusion of trastuzumab deruxtecan on C1D1, C2D1 and C3D1, measured at any time on C1D8 and C1D15 and before trastuzumab deruxtecan infusion on Day 1 of each subsequent cycle (C4D1 onwards), and at the end of treatment visit and the follow-up visit.

[g] Patients who have Grade 3 or higher (or clinically significant) thrombocytopenia, neutropenia or anaemia in C1 or C2 should continue to have haematology assessments on D1 and D8 in all further treatment cycles

[h] Collect blood samples for troponin (preferably high-sensitivity troponin-T) at Screening, study drug discontinuation, and if at any time a patient reports signs or symptoms suggesting congestive heart failure, myocardial infarction, or other causes of myocyte necrosis. If it is not possible to assess troponin T, sites should assess troponin I instead. All samples for a patient should be assessed using the same Troponin test at the same laboratory throughout the study where feasible.

[i] This may be used for molecular profiling following the availability of a well-validated plasma NGS panel. The timing will be clarified in the Pathology and Genomics Testing Manual

[j] If not taken at screening the sample can be taken at any visit until the final study visit.

[k] Durvalumab PK samples are to be taken prior to the infusion of trastuzumab deruxtecan (up to 2 hours pre-dose); trastuzumab deruxtecan C1D1 PK samples are to be taken prior to the infusion of trastuzumab deruxtecan (up to 2 hours pre-dose) within 15 minutes after the end of trastuzumab deruxtecan infusion, and 5 hours after infusion of trastuzumab deruxtecan (±2 hours post dose); trastuzumab deruxtecan C2D1 and C4D1 PK samples are to be taken prior to the infusion of trastuzumab deruxtecan (up to 2 hours pre-dose) within 15 minutes after the end of trastuzumab deruxtecan infusion.

[l] For patients who receive chloroquine or hydroxychloroquine, additional PK blood draws will be taken as described in Section 11.

[m] Samples to be collected before trastuzumab deruxtecan infusion.

[n] Spirometry at baseline is required. [Minimum requirement of: FVC (L), FVC % predicted, FEV_1 (L), FEV_1 % predicted, FEV_1/FVC. Optional components to include: PEF, FEV6, TLC, DLCO]. DLCO will be performed/encouraged if feasible, but for patients with prior severe and/or clinically significant pulmonary disorders DLCO is a requirement.

[o] Ad hoc collection of survival status may be requested for overall survival analyses

[p] Following the final data cut-off for the module CSR (see Section 9.4.2 of the core protocol), any patients on study treatment may continue on treatment and should be assessed for safety according to standard local clinical practice. Study drug administration, SAE reporting and related safety assessment data should be recorded in the eCRF until 90 days after study drug discontinuation, when the patient will end participation in the study. The other assessments for the study will no longer be performed and those data will no longer be collected; the tumour evaluations will be performed as per standard of care. The survival follow-up will no longer be conducted.

[q] ECG will be taken in triplicate at screening and before initiation of study therapy on Day 1 of each cycle. Subsequent ECGs will be performed in triplicate in close succession only if an abnormality is noted. ECGs will be taken while in a supine/semi-recumbent position. If ECG is abnormal follow institutional guideline.

[r] Whole blood to be taken every cycle for the first 3 cycles and then at every radiographic assessment thereafter visit (every 6 weeks ±1 week for the first 24 weeks relative to the start of combination therapy (C1D1), then every 8 weeks ±1 weeks) in all patients (at pre-dose on dosing day) until disease progression (or study treatment discontinuation).

[s] On-treatment biopsy is not required if a fresh tumour sample is not collected at pre-screening.

[t] A + 2-day window is allowed for durvalumab and trastuzumab administration.

A main screening assessments specific for Module 6 (additional to those in the core protocol); ADA anti-drug antibodies; AE adverse event; APTT activated partial thromboplastin time; C cycle; CD8+ cytotoxic T cell; CSR clinical study report; CT computed tomography; CCI [redacted] D day; ECG electrocardiogram; eCRF electronic Case Report Form; DLCO diffusion lung carbon monoxide; ECOG Eastern Co-operative Oncology Group; FEV_1 forced expiratory volume in 1 second; FEV_6 forced expiratory volume in 6 seconds; FVC forced vital capacity; HRCT high resolution computed tomography; INR international normalised ratio; LVEF left ventricular ejection fraction; MUGA multigated acquisition scan; RECIST 1.1 Response Evaluation Criteria in Solid Tumours 1.1; MRI magnetic resonance imaging; PBMC peripheral blood mononuclear cell; PD-1 programmed cell death-1; PEF peak expiratory flow; PK pharmacokinetics; Q12W every 12 weeks; Q24W every 24 weeks; SAE serious adverse event; SpO_2 peripheral oxygen saturation; TCR T-cell receptor repertoire; TLC total lung capacity; TSH thyroid-stimulating hormone; T_3 triiodothyronine; T_4 thyroxine.

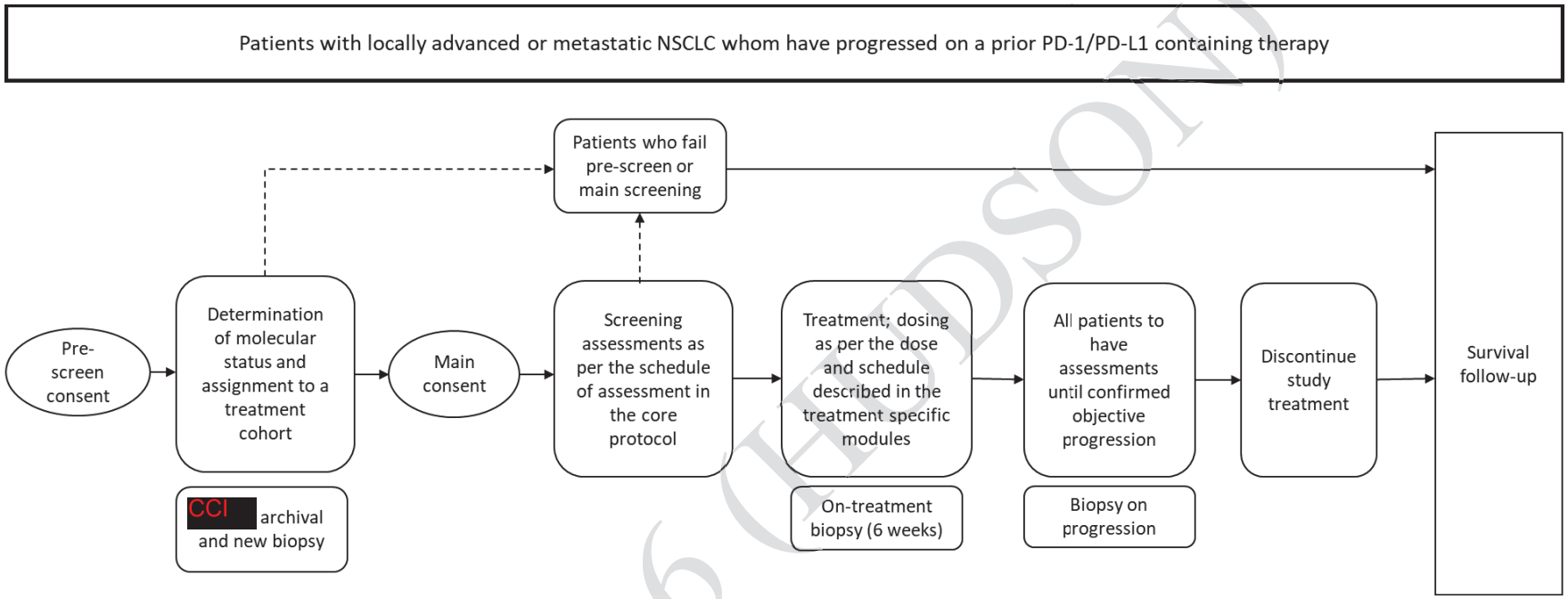
1.2 Synopsis

Please refer to Section 1.2 of the core protocol.

1.3 Schema

The general study design is summarised in Figure 1.

Figure 1 Study design



Note, from implementation of protocol v10.0, survival follow-up of screen failures is no longer applicable.
Additional screening assessments for Module 6 are shown in Table 1.
CCI ; NSCLC, non-small cell lung cancer; PD-1, programmed cell death-1; PD-L1, programmed cell death ligand 1.

1.3.1 Safety run-in

A safety run-in will be conducted, in which approximately 6 patients will be followed for 2 cycles to assess safety (Figure 2). The study procedures and safety assessments undertaken for the first 2 cycles will be as per the SoA (Table 1). The safety run-in can comprise patients that are allocated to the either the HER2 expression cohort (A.6.HER2e) or the HER2 mutation cohort (A.6.HER2m) to provide the earliest opportunity to assess tolerability of the combination in 6 patients.

After administration of the first dose to the first patient, at least 24 hours must be allowed before administration to the second patient in case of unexpected acute toxicity.

A patient will be evaluable for dose-limiting toxicity (DLT) safety assessment if they have received at least 75% of the scheduled dose. Any of the 6 patients who withdraw during the safety run-in can be replaced, except if they dose reduced or discontinued due to toxicity.

After the completion of 6 weeks (2 cycles) dosing in the first 6 evaluable patients in Module 6, all safety data (including, but not limited to, DLTs and AESIs), will be assessed to ensure the combination is safe and tolerable. This assessment, and subsequent go-ahead to continue dosing in the module, at a revised dose if indicated, will be undertaken by a Safety Review Committee (SRC). The role and responsibilities of SRC members, as well as the purpose and timing of the SRC meetings are described in the SRC Charter (Appendix A).

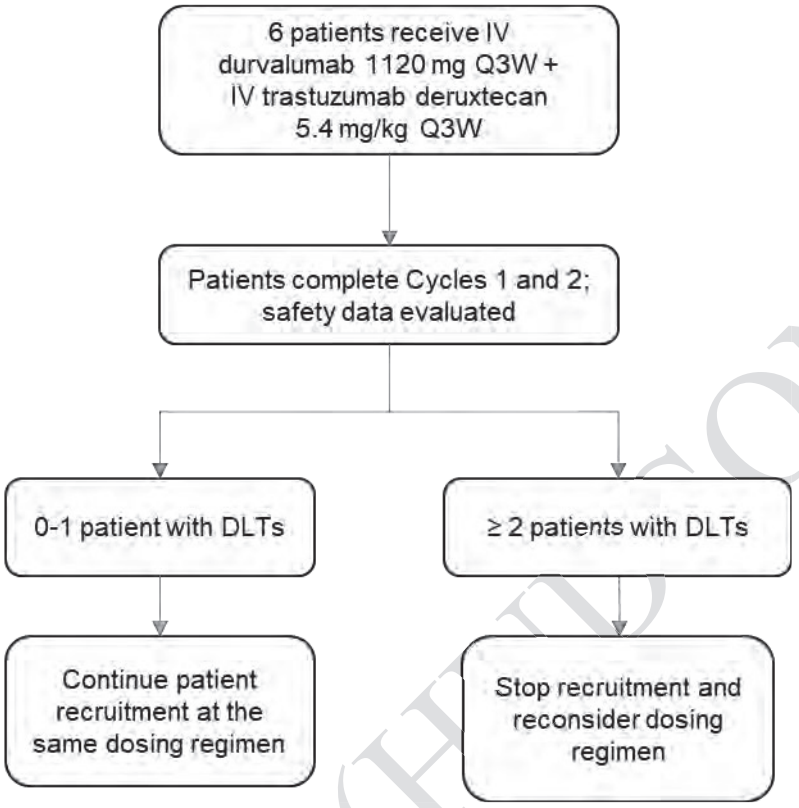
The purpose of the safety run-in is confirmation of the dose of trastuzumab deruxtecan and durvalumab in combination. Recruitment to Module 6 will be paused whilst the SRC convenes to assess the safety data at the end of the safety run-in phase. Additional patients may be dosed once this decision has been taken. If the combination dose is tolerated, patients from the safety run-in phase will contribute to the required enrolment total for the A.6.HER2e and A.6.HERm cohorts.

DLT rules

The following DLT rules will be used in the safety run-in (6 evaluable patients):

- 0 to 1 patient with DLTs: continue recruitment
- ≥2 patients with DLTs: stop recruitment.

Figure 2 Safety run-in flow chart



DLT dose-limiting toxicity; IV intravenous; Q3W every 3 weeks

DLT is defined as any treatment-emergent adverse event (TEAE) not attributable to disease or disease-related processes that occurs during the DLT evaluation period (Day 1 to Day 42 in Cycles 1/2) and is Grade 3 or above according to National Cancer Institute Common Terminology Criteria for Adverse Event (NCI-CTCAE) version 4.03, with the exceptions as defined below. A comprehensive safety review of all safety data in the first 6 patients will be performed before additional patients can be enrolled. This review will include all safety data from these 6 patients up until the sixth patient has completed 2 cycles of study treatment.

For haematological toxicities, a DLT is defined as follows:

- Grade 4 neutrophil count decreased lasting >7 days
- Febrile neutropenia
- Grade 4 anaemia
- Grade 4 platelet count decreased
- Grade 3 platelet count decreased lasting >7 days
- Grade 3 platelet count decreased with clinically significant haemorrhage
- Grade 4 lymphocyte count decreased lasting ≥14 days

Note: Administration of haemopoietic growth factors within the DLT assessment period is at Investigator discretion according to local practice and as required for patient safety. If it is deemed necessary to use prophylactic and/or therapeutic G-CSF during the DLT period to support the patient, it will be allowed but it will constitute either DLT or non-evaluable per the dissertation of SRC.

For hepatic organ toxicities, a DLT is defined as follows:

- Grade 4 aspartate aminotransferase (AST) or alanine aminotransferase (ALT) increased
- AST or ALT ≥3 x upper limit of normal (ULN), if accompanied by Grade ≥2 blood bilirubin increased
- In patients without liver metastases, AST or ALT >5 x ULN lasting >3 days
- In patients with liver metastases, AST or ALT >5 x ULN lasting >3 days, if the baseline level was ≤3 x ULN
- In patients with liver metastases, AST or ALT >8 x ULN lasting >3 days, if the baseline level was >3 x ULN

For non-haematological, non-hepatic major organ toxicities, a DLT is defined as follows:

- Symptomatic congestive heart failure (CHF)
- Left ventricular ejection fraction (LVEF) decline to <40% or >20% drop from baseline
- Other Grade ≥3 non-haematological, non-hepatic major organ toxicities.

The following TEAEs are NOT considered DLTs:

- Grade 3 fatigue lasting <7 days
- Grade 3 nausea, vomiting, diarrhoea, or anorexia that has resolved to Grade ≤2 within 3 days
- Isolated laboratory findings not associated with signs or symptoms including Grade 3/4 alkaline phosphatase (ALP) increased, hyperuricemia, serum amylase increased, and lipase increased, and Grade 3 hyponatremia lasting <72 hours developed from Grade 1 at baseline
- Grade 3 lymphocyte count decreased.

If any of the above toxicities is observed during the DLT evaluation period, whether or not the toxicity is regarded as DLT will be determined based on consultation between the Investigator and Sponsor. In addition, with regard to other toxicities that hinder the conduct of the scheduled study treatment or anaemia with blood transfusion, whether or not they are regarded as DLT will be determined based on consultation between the Investigators and Sponsor.

2. INTRODUCTION

Study D6185C00001 (HUDSON) is a Phase II, open-label, multi-centre umbrella study in patients who have received an anti-programmed cell death-1 (PD-1)/anti-programmed cell death-ligand 1 (PD-L1) containing therapy and a platinum-doublet regimen for locally advanced or metastatic non-small cell lung cancer (NSCLC) either separately or in combination. The patient must have had disease progression on a prior line of anti-PD-1/PD-L1 therapy. The modular design allows the evaluation of the efficacy, safety, and tolerability of multiple study drugs. This module to the core study protocol describes Module 6, which will investigate the efficacy, safety, and tolerability of durvalumab administered in combination with trastuzumab deruxtecan (DS-8201a).

2.1 Study rationale

As described in Section 2.2 of the core protocol, immune checkpoint inhibitors targeting the PD-1/PD-L1 pathway have shown significant activity in the first- and second-line treatment settings in patients with NSCLC. However, it is becoming evident that there is a new and significant patient population emerging that does not respond to anti-PD-1/PD-L1 containing therapy (primary resistance) or progresses during anti-PD-1/PD-L1 containing therapy (acquired resistance). There is currently no established therapy for patients who have developed resistance to PD-1/PD-L1 and platinum-doublet therapies, and novel treatments for these patients are urgently needed.

The aim of this umbrella study (D6185C00001) is to investigate multiple study drugs for the treatment of NSCLC in molecularly matched and non-matched patient populations after failure of immune checkpoint inhibitors, to identify patient populations who may respond favourably to novel anti-tumour therapies.

2.2 Background

Durvalumab and trastuzumab deruxtecan are both currently in clinical development as anti-cancer therapies in a variety of malignancies.

Durvalumab as a weight-based regimen of 10 mg/kg every 2 weeks (Q2W) has been approved for use in the treatment of patients with urothelial carcinoma (UC). On 16 February 2018, durvalumab was approved in the US for the treatment of patients with unresectable Stage III NSCLC. On 21 September 2018, durvalumab was approved in the European Union (EU) for the treatment of locally advanced, unresectable NSCLC in adults whose tumours express PD-L1 on ≥1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy. As of 12 July 2019, durvalumab is approved in over 45 countries for NSCLC. On 27 March 2020, the Food and Drug Administration approved durvalumab in combination with etoposide and either carboplatin or cisplatin as first-line treatment of patients with extensive-stage small cell lung cancer.

Trastuzumab deruxtecan is currently being evaluated in Phase I-III for the treatment of a variety of advanced human epidermal growth factor receptor 2 (HER2)-positive cancer types, including breast cancer, gastric cancer, colorectal cancer, and non-squamous NSCLC.

Module 6 will investigate both agents in combination, to test the hypothesis that the combination will result in complementary anti-tumour activity. Brief background on durvalumab and trastuzumab deruxtecan, including their mechanisms of action, is provided below. For detailed descriptions of the chemistry, pharmacology, efficacy, and safety of durvalumab and trastuzumab deruxtecan, refer to the respective Investigator's Brochures (IBs).

The study will recruit biomarker-matched patients (see Section 4.1). The biomarkers of interest are HER2 expression and HER2 mutation.

2.2.1 Durvalumab

2.2.1.1 Overview of durvalumab

Expression of PD-L1 protein is an adaptive immune response that helps tumours evade detection and elimination by the immune system. PD-L1 can be induced by inflammatory signals (eg, interferon-gamma) and can be expressed on both tumour cells and tumour-associated immune cells in tumour microenvironment. PD-L1 blocks T-cell function and activation through interaction with PD-1 and CD80 (B7.1). By binding to its receptors, PD-L1 reduces cytotoxic T-cell activity, proliferation, and cytokine production. Durvalumab is a fully human, high affinity, immunoglobulin G1 kappa monoclonal antibody that selectively blocks the interaction of PD-L1 with PD-1 and cluster of differentiation (CD)80 (B7.1) while leaving PD-1/programmed cell death ligand-2 interaction intact. Durvalumab does not induce antibody dependent cell-mediated cytotoxicity. Selective blockade of PD-L1/PD-1 and PD-L1/CD80 interactions enhances antitumour immune responses. These antitumour responses may result in tumour elimination.

Durvalumab is approved in a number of territories including the US, EU, Japan, Canada and Brazil under the brand name IMFINZI™ Injection.

The recommended dose as per the IMFINZI package insert is 10 mg/kg administered as an IV infusion over 60 minutes Q2W.

For more information, please refer to the latest version of the durvalumab Investigator's Brochure.

2.2.1.2 Durvalumab data

To date, durvalumab has been given to more than 12000 patients as part of ongoing studies either as monotherapy or in combination with other anticancer agents. Details on the safety profile of durvalumab monotherapy are summarised below. Refer to the current durvalumab

IB for a complete summary of pre-clinical and clinical information including safety, efficacy, and pharmacokinetics (PK).

Clinical activity in locally advanced NSCLC

The efficacy of durvalumab was evaluated in the PACIFIC Study, a randomised, double-blind, placebo-controlled, multicentre study in 713 patients with histologically or cytologically confirmed locally advanced, unresectable NSCLC. Patients had completed definitive platinum-based chemoradiation within 1 to 42 days prior to initiation of the study and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Ninety-three percent of patients had received a total dose of 54 to 66 Gy of radiation. The study excluded patients who had progressed following concurrent chemoradiation therapy, patients with active or prior documented autoimmune disease within 2 years of initiation of the study; a history of immunodeficiency; a history of severe immune-mediated adverse reactions; medical conditions that required systemic immunosuppression, except physiological dose of systemic corticosteroids; active tuberculosis or hepatitis B or C or HIV infection or patients receiving live attenuated vaccine within 30 days before or after the start of durvalumab. Patients were randomised 2:1 to receive 10 mg/kg durvalumab (n=476) or 10 mg/kg placebo (n=237) via intravenous (IV) infusion Q2W for up to 12 months or until unacceptable toxicity or confirmed disease progression. Randomisation was stratified by gender, age (<65 years vs. ≥65 years) and smoking status (smoker vs. nonsmoker). Patients with disease control at 12 months were given the option to be re-treated upon disease progression. Tumour assessments were conducted every 8 weeks for the first 12 months and then every 12 weeks thereafter.

The demographics and baseline disease characteristics were well balanced between study arms. Baseline demographics of the overall study population were as follows: male (70%), age ≥65 years (45%), White (69%), Asian (27%), other (4%), current smoker (16%), past-smoker (75%), and never smoker (9%), World Health Organisation (WHO)/ECOG PS 0 (49%), WHO/ECOG PS 1 (50%). Disease characteristics were as follows: Stage IIIA (54%), Stage IIIB (44%), histological subgroups of squamous (47%), non-squamous (53%), PD-L1 expression in tumour cells (TC)≥25% (22%), PD-L1 expression TC<25% (41%). (PD-L1 status was retrospectively analysed using the Ventana PD-L1 [SP263] Assay in 451 patients with available samples, taken prior to concurrent chemoradiation therapy).

At the time of the interim progression-free survival (PFS) analysis, the median PFS by blinded independent central review (BICR) was significantly longer with durvalumab treatment (16.8 months) compared with placebo (5.6 months); hazard ratio 0.52; 98.9% CI: 0.39, 0.70; p<0.0001. At the time of the interim overall survival (OS) analysis, the median OS was not reached for the durvalumab arm and was 29.1 months for the placebo arm; hazard ratio, 0.69; 95% CI, 0.55, 0.86). The 36-month OS rate was 57.0% with durvalumab vs 43.5% with placebo.

Clinical activity in recurrent and metastatic NSCLC

Based on current data from the ongoing Study CD-ON-MEDI4736-1108 (NCT01693562), evidence of clinical activity with durvalumab has been observed. The following responses were observed in patients with NSCLC.

Overall, clinical activity was observed in both the PD-L1 high (defined as having tumour cells [TC] ≥25%) and PD-L1 low/negative (defined as TC <25%) subgroups, however, patients with PD-L1 high tumours had higher objective response rates (ORRs).

The ORR per BICR was 21.8% and 6.4% in patients with PD-L1 high and low/negative tumours, respectively, and 15.3% in the overall population regardless of PD-L1 expression. The ORR was 25.9%, 14.3% and 11.5% in the 1L, 2L and 3L+ cohorts, respectively. Median duration of response (DoR) was 17.74 months. Median OS was 12.4 months; median OS was 21.0, 11.8 and 9.3 months in the 1L, 2L and 3L+ cohorts, respectively. The OS rate at 24 months was 29.6%.

The ATLANTIC study in third-line or higher NSCLC showed higher ORR and survival outcomes in high PD-L1 positive patients. Across cohorts the ORR ranged from 3 to 43%, median PFS ranged from 1.8 to 5.5 months and median OS ranged from 5.9 to 13.6 months but was not reached at the time of initial reporting in the >90% PD-L1 expressors. The ORR and survival outcomes reported in durvalumab studies are in keeping with other similar agents targeting the PD-1/PD-L1 axis (Garassino et al 2017).

Preliminary efficacy data from the MYSTIC study in first-line advanced or metastatic NSCLC showed that in PD-L1 high (≥25% TC) NSCLC, median PFS by BICR was 4.7 months for durvalumab monotherapy and 5.4 months for chemotherapy; hazard ratio of 0.87; 99.5% CI: 0.593, 1.285; p=0.324. The median OS was 16.3 months for the durvalumab arm and 12.9 months for the chemotherapy arm; hazard ratio for death was 0.76; 97.54% CI: 0.564, 1.019; p=0.036. The 24-month OS rate was 38.3% vs 22.7% and the 12-month PFS rate was 32.3% vs 14.3% for the durvalumab and chemotherapy arms respectively. When durvalumab was administered in combination with tremelimumab, the median PFS by BICR was 3.9 months for durvalumab + tremelimumab and 5.4 months for chemotherapy; hazard ratio of 1.05; 99.5% CI: 0.722, 1.534; p=0.705. The median OS was 11.9 months for the durvalumab + tremelimumab arm and 12.9 months for the chemotherapy arm; hazard ratio for death was 0.85; 98.77% CI: 0.611, 1.173; p=0.202. The 24-month OS rate was 35.4% vs 22.7% and the 12-month PFS rate was 25.8% vs 14.3% for the durvalumab + tremelimumab and chemotherapy arms respectively.

Immuno-oncology agents targeting the PD-1/PD-L1 pathway have demonstrated activity as monotherapy and in combination with chemotherapy in patients who are immunotherapy-naïve. However, the present study will recruit patients who either have primary resistance to

anti-PD-1/PD-L1 therapy or who developed acquired resistance while on anti-PD-1/PD-L1 therapy. Thus, in this immunotherapy-resistant setting, durvalumab will be administered in combination with an agent that has a different and complementary mechanism of action in order to maximise the likelihood of clinical activity.

2.2.2 Trastuzumab deruxtecan

2.2.2.1 Overview of trastuzumab deruxtecan

Trastuzumab deruxtecan (DS-8201a, T-DXd, ENHERTU®) is an antibody-drug conjugate that targets HER2. The anti-HER2 component of T-DXd is a humanized IgG1 monoclonal antibody that has the same amino acid sequence of trastuzumab. DXd is a derivative of exatecan (Abou-Alfa et al 2006, Cheverton et al 2004, De Jager et al 2000), a topoisomerase I inhibitor that is used as the drug component. Therefore, Trastuzumab deruxtecan is composed of the monoclonal antibody and DXd bound together by a maleimide tetrapeptide linker.

Trastuzumab deruxtecan is expected to inhibit tumour growth for the following reasons: it exhibits antibody-dependent cellular cytotoxic activities and Akt phosphorylation inhibition when it binds to HER2; and DXd that is released from trastuzumab deruxtecan after internalization induces apoptosis by inhibiting topoisomerase I. In vitro studies indicate that T-DXd exhibits HER2-expression-dependent cell growth inhibitory activity, and in vivo studies using tumour-bearing mouse models suggest that the administration of trastuzumab deruxtecan results in the regression of HER2-positive tumours.

Trastuzumab emtansine (T-DM1; Kadcyla®) is an antibody-drug conjugate targeting HER2 that has been approved in the United States, Europe, and Japan for the indication of HER2-positive unresectable or recurrent breast cancer. Emtansine, which inhibits tubulin polymerization, is used as the drug component in T-DM1. Compared to T-DM1, trastuzumab deruxtecan has a different mechanism of action for the drug component (topoisomerase I inhibition vs tubulin polymerization inhibition) with high plasma stability, higher drug-to-antibody ratio (DAR, approximately 8) with a homogenous distribution, and the bystander effect. A bystander anti-tumour effect is another key factor to potentially improve the antitumor activity in heterogeneous tumours. The bystander anti-tumour effect is a cytotoxic effect on neighbouring HER2-antigen negative tumour cells caused by a membrane permeable drug, which is released from the antibody-drug conjugate in target-expressing tumour cells. The released drug of trastuzumab deruxtecan has membrane permeability, whereas that of T-DM1 has been shown to have poor membrane permeability. Therefore, trastuzumab deruxtecan is expected to be effective even in tumours that do not respond or are resistant to T-DM1.

In vivo studies in various mouse xenograft models demonstrated that trastuzumab deruxtecan has greater antitumor activity than T-DM1. The studies also confirmed that trastuzumab

deruxtecan is also active against HER2-low and HER2-heterogeneous tumours that are insensitive to T-DM1.

In summary, trastuzumab deruxtecan incorporates a novel antibody-drug conjugate linker technology to deliver a novel topoisomerase I inhibitor chemotherapy to HER2-expressing tumours. Trastuzumab deruxtecan is therefore expected to exhibit activity in a broad patient population.

For more information, please refer to the latest version of the trastuzumab deruxtecan Investigator's Brochure.

2.2.2.2 Trastuzumab deruxtecan data

As of 08 June 2021, trastuzumab deruxtecan has been evaluated in 27 clinical studies (18 monotherapy studies and 9 combination therapy studies). The estimated number of subjects treated with trastuzumab deruxtecan alone or in combination with other anti-cancer therapies, or physician's choice group or comparator, or in expanded access program, or in AstraZeneca sponsored studies is 3462 subjects. Seven studies are complete, and 20 studies are ongoing. The preliminary results from patients with NSCLC are shown below.

NSCLC

In the DS8201-A-U204 (DESTINY-Lung01) study, as of the data cut-off date of 08 June 2021, a total of 181 subjects had received trastuzumab deruxtecan: 49 subjects in Cohort 1, 41 subjects in Cohort 1a (HER2-overexpressing [IHC 3+ or IHC 2+] and 91 subjects in Cohort 2 (HER2-mutated, unresectable and/or metastatic NSCLC). As of 31 May 2020, for Cohort 1 (HER2-overexpressing; n = 49) and Cohort 2 (HER2-mutated; n = 66), respectively, a pre-defined interim analysis showed a confirmed ORR by independent central review (ICR) of 24.5% and 50.0%, a median DoR of 6.0 months and 12.0 months, and an estimated median PFS of 5.4 months and 13.8 months.

As of 08 June 2021, 181 (100%) subjects experienced at least one TEAE. The most frequently (≥ 20% of subjects) reported TEAEs were nausea (128 [70.7%] subjects), decreased appetite (73 [40.3%]), vomiting (67 [37.0%]), diarrhoea (66 [36.5%]), fatigue (66 [36.5%]), constipation (60 [33.1%]), alopecia (57 [31.5%]), anaemia (56 [30.9%]), dyspnoea (40 [22.1%]), neutrophil count decreased (40 [22.1%]), and weight decreased (39 [21.5%]).

A total of 123 subjects (68.0%) experienced ≥ Grade 3 TEAEs. The most commonly (≥10% of subjects) reported ≥ Grade 3 event was: neutrophil count decreased (27 [14.9%] subjects.

A total of 56 (30.9%) subjects had TEAEs associated with study drug discontinuation. The following events led to study treatment discontinuation: pneumonitis (23), disease progression (8), ILD (6), pneumonia (2), ejection fraction decreased, *Pneumocystis jirovecii* pneumonia, respiratory failure, proctalgia, mental status changes, ileus, delirium, myocardial infarction,

fatigue, diarrhoea, lung disorder, neutrophil count decreased, sepsis, dyspnoea, acute pulmonary oedema, platelet count decreased, and weight decreased (1 per subject).

A total of 35 (19.3%) subjects had events that were adjudicated as drug-related ILD/pneumonitis, including 5 (2.8%) Grade 1, 21 (11.6%) Grade 2, 3 (1.7%) Grade 3 and 6 (3.3%) Grade 5.

A total of 30 (16.6%) subjects experienced TEAEs associated with an outcome of death and the following events were reported: disease progression (8), pneumonitis (2), sudden death (2), acute pulmonary oedema, bronchospasm, disease complication, dyspnoea, hydrocephalus, intestinal perforation, *Pneumocystis jirovecii* pneumonia, respiratory failure, seizure and sepsis (1 per subject).

Serious TEAEs that were captured in the safety database as of the 08 June 2021 DCO are presented in Table 2.

Table 2 Serious treatment-emergent adverse events in Study DS8201-A-U204 (DESTINY-Lung01) through 08 June 2021

MedDRA System Organ Class[a]	MedDRA Preferred Term	Number of events
Infections and infestations	Oesophageal infection	1
	Enterocolitis infectious	1
	Cellulitis	1
	Pneumonia	7
	COVID-19 pneumonia	1
	Respiratory tract infection	2
	Empyema	1
	Pneumocystis jirovecii pneumonia	1
	Sepsis	1
	Bacteraemia	1
	Septic shock	1
	Skin infection	1
	Staphylococcal pneumonia	1
	Staphylococcal bacteraemia	1
	Urinary tract infection	1
Blood and lymphatic system disorders	Thrombocytopenia	1
Psychiatric disorders	Confusional state	1
	Delirium	1
	Mental status changes	2
Nervous system disorders	Ataxia	1

Table 2 Serious treatment-emergent adverse events in Study DS8201-A-U204 (DESTINY-Lung01) through 08 June 2021

MedDRA System Organ Class[a]	MedDRA Preferred Term	Number of events
	Syncope	1
	Hepatic encephalopathy	1
	Hydrocephalus	1
	Central nervous system necrosis	2
	Presyncope	1
	Seizure	4
	Partial seizures	2
Vascular disorders	Deep vein thrombosis	1
	Hypotension	2
Respiratory, thoracic and mediastinal disorders	Dyspnoea	6
	Bronchospasm	1
	Wheezing	1
	Hypoxia	3
	Haemoptysis	1
	Pneumonitis	13
	Interstitial lung disease	3
	Pleural effusion	3
	Pneumothorax	1
	Pulmonary oedema	1
	Acute pulmonary oedema	1
	Respiratory failure	1
Gastrointestinal disorders	Diarrhoea	3
	Small intestinal obstruction	1
	Duodenal stenosis	1
	Duodenal ulcer haemorrhage	1
	Gastrointestinal mobility disorder	1
	Intestinal obstruction	1
	Ileus	1
	Haemorrhoids	1
	Rectal haemorrhage	1
	Small intestinal haemorrhage	1
	Intestinal perforation	1
	Vomiting	5

Table 2 Serious treatment-emergent adverse events in Study DS8201-A-U204 (DESTINY-Lung01) through 08 June 2021

MedDRA System Organ Class[a]	MedDRA Preferred Term	Number of events
	Nausea	3
	Upper gastrointestinal haemorrhage	1
	Intra-abdominal haematoma	1
	Gastrointestinal haemorrhage	1
	Oesophageal obstruction	1
Hepatobiliary disorders	Cholangitis	1
Musculoskeletal and connective tissue disorders	Bone pain	1
	Osteoarthritis	1
Renal and urinary disorders	Acute kidney injury	1
General disorders and administration site conditions	Fatigue	2
	Asthenia	1
	Sudden death	2
	Pyrexia	1
	Disease progression	17
	Disease complication	1
	Oedema peripheral	1
	Pain	1
	Non-cardiac chest pain	1
Investigations	Electrocardiogram T wave abnormal	1
	Troponin increased	1
	Troponin I increased	1
Injury, poisoning and procedural complications	Fall	1
	Radiation necrosis	1
	Transfusion reaction	1

[a] MedDRA Version 24.0
Total number of treated subjects as of the IB cut-off date of 08 June 2021 was 181.
MedDRA, Medical Dictionary for Regulatory Activities.
Source: Preliminary data from sponsor safety database as of 08 June 2021.

Efficacy and safety data for other cancer types (breast cancer, gastric cancer, colorectal cancer, and other tumours) can be found in the trastuzumab deruxtecan IB.

2.3 Benefit/risk assessment

2.3.1 Trastuzumab deruxtecan benefit/risk

Trastuzumab deruxtecan is under development for the treatment of HER2-expressing cancers and HER2-mutant tumours. Based on clinical observations in the Phase I study (Study DS8201-A-J101) and Phase II studies (DS8201-A-U201 [DESTINY-Breast01] and DS8201-A-J202 [DESTINY-Gastric01], trastuzumab deruxtecan demonstrates antitumor activity in HER2-expressing and HER-2 mutant cancers, including breast cancer and gastric cancer (see Section 2.2.2.2).

From the completed DS8201-A-U201 (DESTINY-Breast01) study (data cut-off: 01 August 2019), the overall efficacy results in subjects with HER2-positive breast cancer at 5.4 mg/kg demonstrated a confirmed ORR and DoR by ICR of 60.9% and 14.8 months, respectively. From the completed DS8201-A-J202 (DESTINY-Gastric01) study (data cut-off: 08 November 2019) in subjects with HER2-positive gastric cancer, the trastuzumab deruxtecan group was compared with the physician's choice group and demonstrated a significantly higher confirmed ORR by ICR (42.9% versus 12.5%, respectively) and significant improvement in median OS with 12.5 months for trastuzumab deruxtecan versus 8.4 months for physician's choice at the pre-specified interim analysis (adjusted OS hazard ratio = 0.59, stratified log-rank test, P = 0.0097; O'Brien Fleming boundary = 0.0202). From the completed DS8201-A-J101 study (data cut-off: 01 February 2019), the confirmed ORR by ICR among the subjects with HER2-low breast cancer was 37.0% and the overall efficacy results in subjects with other cancers demonstrated a confirmed ORR by ICR of 29.5%.

Based on data from clinical trials, toxicities considered to be associated with administration of trastuzumab deruxtecan include the important identified risks of ILD/pneumonitis and neutropenia (including febrile neutropenia). Other identified risks for trastuzumab deruxtecan are infusion-related reactions, haematological adverse events, (leukopenia, lymphopenia, anaemia, thrombocytopenia), pulmonary/respiratory adverse events (cough, dyspnoea, upper respiratory tract infection, epistaxis), gastrointestinal adverse events (abdominal pain, constipation, diarrhoea, dyspepsia, nausea, stomatitis, vomiting), hepatic adverse events (hepatic function abnormality, ALT, AST and alkaline phosphatase increased) skin adverse events (alopecia, rash, pruritus), blood bilirubin increased, pneumonia, dry eye, dehydration, hypokalaemia, decreased appetite, dizziness, fatigue, peripheral oedema, pyrexia and headache.

Based on the available pre-clinical data, review of the cumulative literature, and reported toxicities for the same class of agents, the important potential risks for trastuzumab deruxtecan are LVEF decrease and embryo-foetal toxicity. Keratitis is considered a potential risk for trastuzumab deruxtecan.

ILD/pneumonitis and LVEF decreased are considered to be AESIs.

T-DXd has not been studied in subjects with severe/moderate hepatic impairment or severe renal impairment.

HER2-targeted agents

Several agents, that target HER2 and prevent its activation or heterodimerization, have been developed and marketed for the treatment of HER2-positive cancers. These include the monoclonal antibodies trastuzumab (Herceptin®) and pertuzumab (Perjeta®), the antibody-drug conjugate T DM1 (Kadcyla®), and HER1 and 2-associated tyrosine kinase inhibitor, lapatinib (Tykerb®) and neratinib (Nerlynx®). The safety profile of these HER2-targeted agents has been well described. The main safety risks identified in subjects receiving HER2-targeted products are described below; these could potentially be expected to occur in subjects receiving trastuzumab deruxtecan.

- **Cardiotoxicity:** Patients treated with trastuzumab are at increased risk for developing CHF (New York Heart Association [NYHA] class II-IV) or asymptomatic cardiac dysfunction, including LVEF decrease. Cardiac dysfunction, mainly asymptomatic LVEF decrease, has also been observed with pertuzumab in combination with trastuzumab. Similarly, cardiac dysfunction has been observed in patients receiving T-DM1, at a lower incidence than in trastuzumab-treated subjects. Majority of cases have been asymptomatic decreases in LVEF. Left ventricular dysfunction has also been observed with margetuximab. Cardiac dysfunction with lapatinib has occurred mainly in subjects receiving the combination of trastuzumab and lapatinib and has consisted of predominantly asymptomatic LVEF decrease.
- **Pulmonary toxicity:** Cases of pulmonary toxicity, including ILD and pneumonitis, have been observed in subjects receiving trastuzumab, T-DM1, and lapatinib. Occasionally these cases have been severe in nature and have resulted in fatal outcomes. Risk factors associated with ILD include prior or concomitant therapy with other anti-neoplastic therapies known to be associated with it such as taxanes, gemcitabine, vinorelbine and radiation therapy.
- **Hypersensitivity/infusion-related reactions:** The administration of therapeutic proteins is associated with a risk of hypersensitivity and/or infusion reactions. Hypersensitivity/infusion-related reactions have been reported with trastuzumab, pertuzumab, T-DM1 and margetuximab. These can range from mild reactions to severe anaphylactic shock with fatal outcome as has been the case for trastuzumab.
- **Hepatic toxicity:** Cases of hepatic toxicity have occurred with T-DM1, lapatinib, and trastuzumab. In subjects receiving T-DM1 hepatic toxicity has manifested mainly as transient asymptomatic liver transaminase elevations, although serious cases of drug-induced liver failure and nodular regenerative hyperplasia have also been reported. Lapatinib has also been associated with serious cases of drug-induced liver injury.
- **Haematological toxicity:** Haematological toxicity has been observed with all HER2-targeted therapies. Neutropenia, febrile neutropenia, leukopenia and anaemia have occurred commonly with trastuzumab, pertuzumab and T-DM1. Thrombocytopenia, including Grade 3 and 4, is a common occurrence in T-DM1 treated subjects. Although rare, serious haemorrhagic events have been reported in the setting of thrombocytopenia.

Lower rates of thrombocytopenia have also occurred with trastuzumab and pertuzumab when used in combination with chemotherapy.

Topoisomerase I inhibitors

MAAA-1181a is a derivative of exatecan (DX-8951f), a topoisomerase I inhibitor. Other products of the same class include irinotecan and topotecan. Exatecan is a campothecin derivative, which has previously been developed by the former Daiichi Pharmaceuticals Co., Ltd. as an anti-cancer therapy.

- The main risks associated with the use of topoisomerase I inhibitors include haematological toxicities and gastrointestinal toxicities. Haematological toxicities, manifesting as neutropenia, febrile neutropenia, anaemia, thrombocytopenia and pancytopenia are commonly observed. An increased risk of infections, including neutropenic colitis and neutropenic sepsis has been reported with these agents.
- Diarrhoea and delayed onset diarrhoea, which can be severe and lead to dehydration, have been associated with topoisomerase I inhibitors. Other significant risks include ILD, liver impairment, immune system disorders and alopecia. Acute cholinergic syndrome, manifesting as diarrhoea and other cholinergic symptoms has been reported with irinotecan.
- The safety profile of exatecan is broadly similar to the safety profile of other topoisomerase I inhibitors, with haematological toxicities and gastrointestinal toxicities being the most significant groups of events.

Given the data available on the efficacy and safety of trastuzumab deruxtecan, the overall benefit/risk is positive.

2.3.2 Durvalumab and trastuzumab deruxtecan in combination

A combination of an immune-mediated therapy, such as durvalumab with a targeted therapy has the potential to increase anti-tumour activity. The immune system can identify and eliminate cancerous cells, but anti-tumour immune response is often held in check by immunosuppressive mechanisms, which can be beneficially altered by the action of durvalumab. One such suppressive mechanism is expression of PD-L1 on the surface of tumour and immune cells. Combination of this anti-PD-L1 immune-mediated therapy and tumour growth inhibition mediated by HER2 could lead to enhanced anti-tumour effects than compared to the efficacy seen with the respective monotherapies. Indeed, trastuzumab deruxtecan is currently being administered in combination with nivolumab in Study DS8201-A-U105 (NCT03523572), (a Phase Ib, multicentre, 2-part, open-label, non-randomized, multiple dose study), in subjects with HER2-expressing advanced breast or urothelial cancer. One further Phase 1 dose-escalation study in which trastuzumab deruxtecan (initial trastuzumab deruxtecan dose of 3.2 mg/kg Q3W with a planned escalation to 5.4 mg/kg Q3W) and pembrolizumab will be administered in combination in patients with locally advanced/metastatic breast or NSCLC (NCT04042701) is being initiated.

Encouraging clinical activity, combined with acceptable and manageable safety, has been seen to date with durvalumab in combination therapy studies. In general, the toxicity profiles of durvalumab and of trastuzumab deruxtecan are non-overlapping; ILD/pneumonitis and infusion-related reactions are the most clinically significant potential exceptions.

Monoclonal antibodies are not metabolised through classical hepatic enzyme pathways, therefore, no PK interaction is anticipated within this study.

As described in Section 2.3 of the core protocol, patients recruited to this study are not expected to have other treatment options apart from monotherapy chemotherapy, such as docetaxel. The survival outcome and toxicity profile of chemotherapy in this setting mean that other active therapies are highly desirable and present a potential advantage for patients.

The study design aims to identify patient populations who may respond favourably to novel anti-tumour therapies. Based upon the available non-clinical and clinical safety data, the limited survival benefit provided by the currently available treatment options to patients, the limited life expectancy due to malignant disease, and the hypothesis of the complementary effect of the 2 agents, the investigation of the potential therapeutic efficacy of the combination of durvalumab with trastuzumab deruxtecan in patients with advanced or metastatic NSCLC is acceptable, and the overall benefit/risk assessment supports the proposed study design. A proposed benefit to seeking signals by this biomarker stratification strategy (ie, in patients expressing HER2 or with HER2 mutation) includes the opportunity to discover potential increased sensitivity to trastuzumab deruxtecan in patients with NSCLC.

3. OBJECTIVES AND ENDPOINTS

Please refer to the core protocol.

4. STUDY DESIGN

4.1 Overall design

This is an open-label, multi-centre, umbrella study in patients who have received an anti-PD-1/PD-L1 containing therapy and a platinum-doublet regimen for locally advanced or metastatic NSCLC either separately or in combination. The patient must have had disease progression on a prior line of anti-PD-1/PD-L1 therapy. For an overview of the study design see Figure 1; further details on the overall design are provided in Section 4 of the core protocol. For details on the study drugs given in Module 6, see Section 6.1 of this module.

Module 6 will evaluate the efficacy, safety, and tolerability of durvalumab (given intravenously [IV]) in combination with trastuzumab deruxtecan (given IV) in 2 cohorts of biomarker-matched patients as follows:

- Cohort A.6 will investigate the safety, tolerability, and anti-tumour activity of durvalumab given IV at 1120 mg Q3W +2 days in combination with trastuzumab deruxtecan 5.4 mg/kg IV (Q3W) +2 days:
  - Cohort A.6.HER2e for patients whose tumours express HER2. The pathology and genomics testing manual describes the criteria for over-expression of HER2. Alternative tests under development for HER2 expression may be deployed for retrospective evaluation of this cohort and this may require additional patients to be enrolled in this module in order to meet the approximately 20 evaluable patients as assessed using the alternative test. The alternative test is intended to be deployed prospectively if the cohort is expanded.
  - Cohort A.6.HER2m for patients whose tumours harbour selected HER2 mutations. Recruitment to the A.6.HER2m cohort will continue in parallel with recruitment to the A.6.HER2e cohort and may stop once the A.6.HER2e cohort is complete. Due to the low prevalence of HER2 mutations, it is likely that less than 20 patients may be dosed in the A.6.HER2m cohort. The analyses and summaries to be produced will be dependent on the number of patients recruited and will be detailed in the SAP.

A study flow diagram is provided in the core protocol (Figure 4).

4.2 Scientific rationale for study design

The study aims to identify patient populations who may respond favourably to novel anti-tumour therapies, and the modular design allows evaluation of the efficacy, safety, and tolerability of multiple study drugs. The study requires an open-label design owing to the different schedules and routes of administration of the study drugs.

The scientific background for inclusion of biomarker-matched cohorts A.6.HER2e (biomarker-matched: HER2 expressors) and Cohort A.6.HER2m (biomarker matched: HER2 mutation) is as follows: Results from clinical studies suggest a potential role of HER2-targeting antibody-drug conjugate in NSCLC. A recent study of T-DM1 in NSCLC based on HER2 immunohistochemistry (IHC) expression showed an ORR of 0% for IHC 2+ tumours, but did demonstrate efficacy with ORR 20% in IHC 3+ tumours (Stinchcombe et al 2017). A separate T-DM1 study reported an ORR of 44% in patients with HER2-mutant NSCLC (Li et al 2018). While there are no direct HER2-targeted therapies approved for NSCLC, further investigation of HER2-targeting strategies are warranted in this patient population.

Patients whose tumours are found to express HER2 but also contain a HER2 mutation will be assigned to the HER2 mutation cohort (A.6.HER2m).

Assignment of HER2 expressors to cohort A.6.HER2e will be using a HER2 immunohistochemistry assay performed centrally in a Clinical Laboratory Improvement Amendments (CLIA)-accredited laboratory. Similarly, patients with relevant HER2 mutations will be identified using a next generation sequencing panel performed at a central CLIA-accredited laboratory. Patients with a relevant HER2 mutation identified using a local test can also be allocated (refer to Pathology and Genomics Testing manual).

4.3 Justification for dose

4.3.1 Justification for durvalumab dose

A durvalumab dose of 20 mg/kg Q4W is supported by in vitro data, pre-clinical activity, clinical PK/pharmacodynamics, biomarkers, and activity data from Study CD-ON-MEDI4736-1108 (hereafter referred to as Study 1108) in patients with advanced solid tumours and from a Phase I study performed in Japanese patients with advanced solid tumours (D4190C00002).

Please refer to the current durvalumab IB for further updates on data from ongoing studies.

PK/Pharmacodynamic data

Based on available PK/pharmacodynamic data from ongoing Study 1108 with doses ranging from 0.1 to 10 mg/kg Q4W or 15 mg/kg Q4W, durvalumab exhibited non-linear (dose dependent) PK consistent with target-mediated drug disposition. The PK approached linearity at ≥ 3 mg/kg Q4W, suggesting near complete target saturation (membrane-bound and

sPD-L1), and further shows that the durvalumab dosing frequency can be adapted to a particular regimen given the linearity seen at doses higher than 3 mg/kg. The expected half-life with doses ≥3 mg/kg Q4W is approximately 21 days. A dose-dependent suppression in peripheral sPD-L1 was observed over the dose range studied, consistent with engagement of durvalumab with PD-L1. A low level of immunogenicity has been observed. No patients have experienced immune-complex disease following exposure to durvalumab. (For further information on immunogenicity, please see the current durvalumab IB).

A population PK model was developed using the data from Study 1108 (doses=0.1 to 10 mg/kg Q2W or 15 mg/kg Q4W; Fairman et al 2014). Multiple simulations indicate that a similar overall exposure is expected following both 10 mg/kg Q4W and 20 mg/kg Q4W regimens, as represented by AUC_{ss} (4 weeks). Median $C_{max,ss}$ is expected to be higher with 20 mg/kg Q4W (~1.5 fold) and median $C_{trough,ss}$ is expected to be higher with 10 mg/kg Q4W (~1.25 fold). Clinical activity with the 20 mg/kg Q4W dosing regimen is anticipated to be consistent with 10 mg/kg Q4W with the proposed similar dose of 20 mg/kg Q4W expected to (a) achieve complete target saturation in majority of patients; (b) account for anticipated variability in PK, pharmacodynamics, and clinical activity in diverse cancer populations; (c) maintain sufficient PK exposure in case of ADA impact; and (d) achieve PK exposure that yielded maximal antitumor activity in animal models.

Given the similar area under the serum drug concentration-time curve (AUC) and modest differences in median peak and trough levels at steady state, the observation that both regimens maintain complete sPD-L1 suppression at trough, and the available clinical data, the 20 mg/kg Q4W and 10 mg/kg Q4W regimens are expected to have similar efficacy and safety profiles, supporting further development with a dose of 20 mg/kg Q4W (or an equivalent dose Q3W).

Clinical data

Refer to the current durvalumab IB for a complete summary of clinical information including safety, efficacy, and PK at the 20 mg/kg Q4W regimen.

Rationale for fixed dosing

A population PK model was developed for durvalumab using monotherapy data Study 1108 (N=292; doses = 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W; solid tumours). Population PK analysis indicated only minor impact of body weight on the PK of durvalumab (coefficient of ≤0.5). The impact of body weight-based (10 mg/kg Q2W) and fixed dosing (750 mg Q2W) of durvalumab was evaluated by comparing predicted steady state PK concentrations (5th, median, and 95th percentiles) using the population PK model. A fixed dose of 750 mg was selected to approximate 10 mg/kg (based on median body weight of ~75 kg). A total of 1000 patients were simulated using body weight distribution of 40 to 120 kg. Simulation results demonstrate that body weight-based and fixed dosing regimens yield similar median

steady state PK concentrations with slightly less overall between-patient variability with fixed dosing regimen.

Similar findings have been reported by others (Narwal et al 2013, Ng et al 2006, Wang et al 2009, Zhang et al 2012). Wang and colleagues investigated 12 monoclonal antibodies and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies (Wang et al 2009). In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-patient variability in PK/pharmacodynamic parameters (Zhang et al 2012).

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar PK exposure and variability, AstraZeneca considered it feasible to switch to fixed dosing regimens.

Combination dose with Q3W chemotherapy regimens

For ease of use and convenience to Investigators and patients in this study, it is intended to administer durvalumab Q3W to align with the treatment intervals of trastuzumab deruxtecan and use a fixed dose of 1120 mg (based on an average body weight of 75 kg, this is equivalent to a weight-based dose of 15 mg/kg Q3W).

The safety of a Q3W dosing schedule of durvalumab (± tremelimumab) in combination with chemotherapy is being explored in a number of ongoing studies including a Canadian Clinical Trials Group (CCTG) dose escalation study NCT02537418.

CCTG Study NCT02537418 is an ongoing Phase I study of durvalumab ± tremelimumab in combination with multiple standard platinum-based chemotherapy regimens in patients with incurable advanced or metastatic cancer. The dose escalation and dose regimens in the study initially included a fixed dose cohort of durvalumab 1125 mg + tremelimumab 56 mg Q3W concurrent with platinum-based doublet chemotherapy and then subsequently a cohort of durvalumab 1500 mg + tremelimumab 75 mg Q3W concurrent with chemotherapy.

Overall, toxicities related to the chemotherapy core regimen appeared as expected in severity and frequency. Overall, across all dose levels, there was no clear dose dependency in any of the reported AEs and there were no DLTs reported per protocol defined criteria (DLT period of 21 days). The overall safety profile appears to be consistent with available safety and tolerability data for durvalumab either as monotherapy or in combination with tremelimumab. In general, all regimens were tolerable and manageable at all dose levels. The study was presented at the World Conference in Lung Cancer in October 2017 (Juergens et al 2017) when 13 patients had been exposed to the fixed durvalumab 1500 mg + tremelimumab 75 mg Q3W dose. There was no evidence of a dose response including the 1500 mg + 75 mg dose cohort in terms of the safety data reported.

In addition, PK modelling has been carried out to predict the effect of switching from a Q4W regimen to a Q3W regimen for durvalumab at a 1500 mg fixed dose. Results suggest that a Q3W regimen would yield similar exposures to Q4W; durvalumab is expected to yield a slightly higher maximum plasma concentration (C_{max}) and minimum plasma concentration (C_{min}) on a 3-week schedule, but a lower AUC. C_{max} values were 660 vs 596 μg/mL, C_{min}, were 144 vs 94 μg/mL, and AUC was 5879 vs 6061 μg/mL for a Q3W and Q4W schedule, respectively. Therefore, PK modelling suggests that a Q3W schedule does not impose a significant increased safety risk based on expected durvalumab exposures.

Based on average body weight of 75 kg, a fixed dose of 1120 mg Q3W durvalumab is included in the current study. In addition to the evidence above showing manageable tolerability and similar exposures to the 1500 mg dose, this dose has been chosen to align with the dose intensity being used in all other modules. A dose of 1120 mg rather than 1125 mg is being used due to the vial sizes that will be available at the time of commercialisation. The dose of durvalumab will not be modified during the study.

4.3.2 Justification for trastuzumab deruxtecan dose

Based on all available information to date, a trastuzumab deruxtecan dose of 5.4 mg/kg Q3W has been chosen for this study. Doses of 5.4 mg/kg and 6.4 mg/kg trastuzumab deruxtecan monotherapy have been tested in clinical studies; both showed efficacy in different tumour types and neither reached the MTD. A numerically higher incidence of ILD/pneumonitis was observed with 6.4 mg/kg compared to 5.4 mg/kg. The combination of durvalumab + trastuzumab deruxtecan is untested in the clinic, and there are very little data on combinations of trastuzumab deruxtecan with other PD-L1 inhibitors (eg, nivolumab and pembrolizumab), so a conservative approach has been taken to evaluate the lowest known efficacious dose of trastuzumab deruxtecan while minimising the risks to patients.

Once the cohort is complete, a benefit-risk assessment will be conducted. Following evaluation of all data, a higher dose of trastuzumab deruxtecan in combination with durvalumab may be studied in the future.

4.4 End of study definition

Please refer to the core protocol.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

Each patient should meet all the inclusion criteria and none of the exclusion criteria for this study in order to be assigned to a study cohort. Under no circumstances can there be

exceptions to this rule. Patients who do not meet the entry requirements are screen failures; refer to Section 5.4 of the core protocol.

5.1 Inclusion criteria (Module 6-specific)

Patients are eligible to be included in the study only if all the following inclusion criteria apply. Please also refer to Section 5.1 of the core protocol for the inclusion criteria applicable to all modules in the study. Additional inclusion criteria applicable to Module 6 only are described in this section.

N-1 Patients must fulfil all the core eligibility criteria.

N-2 Identification of HER2 alterations:

- Cohort A.6.HER2e: HER2 expressing patients (determined by IHC).
- Cohort A.6.HER2m: Selected HER2 mutations (determined by NGS).

N-3 Has adequate washout period before enrolment for chloroquine/ hydroxychloroquine: >14 days.

N-4 Adequate treatment washout period before randomization/enrolment, defined as:

a. Major surgery: ≥ 4 weeks

b. Radiation therapy including palliative stereotactic radiation therapy to chest: ≥ 4 weeks (palliative stereotactic radiation therapy to other areas ≥ 2 weeks).

c. Anti-cancer chemotherapy [(Immunotherapy (non-antibody based therapy)], retinoid therapy, mBC: hormonal therapy: ≥ 3 weeks (≥ 2 weeks or 5 half-lives, whichever is longer, for small-molecule targeted agents such as 5-fluorouracil-based agents, folinate agents, weekly paclitaxel; ≥ 6 weeks for nitrosureas or mitomycin C), ≥ 1 week for tyrosine kinase inhibitors [TKIs] approved for the treatment of NSCLC - baseline computed tomography [CT] scan must be completed after discontinuation of TKI)

d. Antibody-based anti-cancer therapy: ≥ 4 weeks.

New inclusion criteria added in CSP version 10.0:

N-5 Evidence of post-menopausal status or negative serum pregnancy test for females of childbearing potential who are sexually active with a non-sterilized male partner. For women of childbearing potential, a negative result for serum pregnancy test (test must have a sensitivity of at least 25 mIU/mL) must be available at the screening visit and urine beta-human chorionic gonadotropin (β-HCG) pregnancy test prior to each administration of study drug.

Women of childbearing potential are defined as those who are not surgically sterile (ie, underwent bilateral salpingectomy, bilateral oophorectomy, or complete

hysterectomy) or post-menopausal. Women will be considered post-menopausal if they have been amenorrhoeic for 12 months without an alternative medical cause.

N-6 Non-sterilized male patients who are sexually active with a female partner of childbearing potential must use a condom with spermicide from screening to 4 months after the final dose of study drug. Complete heterosexual abstinence for the duration of the study and drug washout period is an acceptable contraceptive method if it is in line with the patient's usual lifestyle (consideration must be made to the duration of the clinical trial); however, periodic or occasional abstinence, the rhythm method, and the withdrawal method are not acceptable.

It is strongly recommended for the female partners of a male patient to also use at least one highly effective method of contraception throughout this period, as described in Table 3 (Section 5.3). Male patients should refrain from fathering a child or freezing or donating sperm from the time of enrolment, throughout the study and for 4 months after the last dose of study drug.

N-7 Female patients must not donate, or retrieve for their own use, ova from the time of enrolment and throughout the study treatment period and for at least 7 months after the final study drug administration. They should refrain from breastfeeding throughout this time. Preservation of ova may be considered prior to enrolment in this study.

5.2 Exclusion criteria (Module 6-specific)

Patients must not enter Module 6 of the study if any of the following exclusion criteria apply. Please also refer to Section 5.2 of the core protocol for the exclusion criteria applicable to all modules in the study. Additional exclusion criteria applicable to Module 6 only are described in this section.

N-1 Patients meet any of the core exclusion criteria.

N-2 Has the following assessment values:

- Platelet count <100 x 10^9/L
- Absolute neutrophil count <1.5 x 10^9/L (granulocyte colony-stimulating factor is not allowed within 1 week prior to screening assessment)
- Haemoglobin < 9 g/dL NOTE: Subjects requiring ongoing transfusions or growth factor support to maintain haemoglobin ≥ 9 g/dL are not eligible. (Red blood cell transfusion is not allowed within 1 week prior to screening assessment)
- Serum albumin <2.5 g/dL
- International normalised ratio, prothrombin time and either partial thromboplastin or activated partial thromboplastin time >1.5 x upper limit of normal (ULN)

- Creatinine clearance (see core protocol exclusion 18f)
- LVEF <50% within 28 days before enrolment.

N-3 Medical history of myocardial infarction within 6 months before enrolment, symptomatic congestive heart failure (New York Heart Association Class II to IV). Patients with troponin levels above ULN at screening (as defined by the manufacturer) and without any myocardial infarction-related symptoms, should have a cardiologic consultation before enrolment to rule out myocardial infarction.

N-4 Has a corrected QT interval (QTcF) prolongation to >470 ms (females) or >450 ms (males) based on an average of screening triplicate 12-lead ECG.

N-5 History of (non-infectious) ILD/pneumonitis, has current ILD/pneumonitis, or where suspected ILD/pneumonitis cannot be ruled out by imaging at screening.

N-6 Exclusion criterion deleted in CSP version 7.0.

N-7 Lung-specific intercurrent clinically significant illnesses including, but not limited to, any underlying pulmonary disorder (ie, pulmonary emboli within 3 months of the study enrolment, severe asthma, severe chronic COPD, restrictive lung disease, pleural effusion etc), and any autoimmune, connective tissue or inflammatory disorders with documented or presumable pulmonary involvement (ie, Rheumatoid arthritis, Sjogren's, sarcoidosis etc) and prior pneumonectomy (complete).

N-8 Exclusion criterion deleted in CSP version 7.0.

N-9 Has unresolved toxicities from previous anticancer therapy, defined as toxicities (other than alopecia) not yet resolved to Grade ≤1 or baseline. Subjects may be enrolled with chronic, stable Grade 2 toxicities (defined as no worsening to > Grade 2 for at least 3 months prior to enrolment and managed with standard of care treatment) that the Investigator deems related to previous anticancer therapy, such as:

- Chemotherapy-induced neuropathy
- Fatigue
- Residual toxicities from prior IO treatment: Grade 1 or Grade 2 endocrinopathies which may include -
  - Hypothyroidism/hyperthyroidism
  - Type 1 diabetes
  - Hyperglycaemia
  - Adrenal insufficiency
  - Adrenalitis
  - Skin hypopigmentation (vitiligo)

N-10 A pleural effusion, ascites or pericardial effusion that requires drainage, peritoneal shunt, or Cell-free and concentrated ascites reinfusion therapy (CART). (Drainage and CART are not allowed within 2 weeks prior to screening assessment).

N-11 Has received a prior anti-HER2 therapy that was discontinued due to toxicity.

N-12 For A.6.HER2e cohort only: has known HER2 mutation (see Pathology and Genomics Testing manual).

N-13 For A.6.HER2m cohort only: Prior treatment with an antibody-drug conjugate which consists of an exatecan derivative that is a topoisomerase I inhibitor.

New exclusion criterion added in CSP version 10.0:

N-14 Previous severe toxicity, which is clinically significant as judged by the investigator, observed during the patient's previous exposure to any of the medications to be used in combination in the study.

For procedures for withdrawal of incorrectly enrolled patients see Section 7.3 of the core protocol.

5.3 Lifestyle restrictions

5.3.1 Restrictions applicable to durvalumab

Patients should not donate blood or blood components while participating in this study and through 90 days after receipt of the final dose of durvalumab or until alternate anticancer therapy is started.

Immunosuppressive medications including, but not limited to systemic corticosteroids at doses beyond 10 mg/day of prednisone or equivalent, methotrexate, azathioprine and tumour necrosis factor alpha blockers are prohibited. Use of immunosuppressive medications for the management of study drug-related AEs and in patients with contrast allergies is acceptable. In addition, use of topical, inhaled and intranasal corticosteroids is permitted (see Table 5).

Live attenuated vaccines within 30 days of durvalumab dosing are prohibited (ie, 30 days prior to the first dose, during treatment with durvalumab and for 180 days post-discontinuation of durvalumab) (see Table 5). Inactivated viruses, such as those in the influenza vaccine or authorised and approved Coronavirus Disease 2019 (COVID-19) vaccines, are permitted (see Table 6).

5.3.2 Restrictions applicable to trastuzumab deruxtecan

The use of tobacco products, e-cigarettes and vaping is strongly discouraged but not prohibited. Prior or current use of these products should be recorded in the eCRF.

Full details of treatment restrictions for patients receiving trastuzumab deruxtecan are provided in Section 6.5.

Reproduction

Female patients of childbearing potential who are sexually active with a non-sterilized male partner must use at least one highly effective method of contraception (Table 3) from the time of screening (those using hormonal methods must have been stable on their chosen form of contraception for 3 months prior to study entry) and must agree to continue using such precautions for 7 months after the last dose of study drug; cessation of birth control after this point should be discussed with a responsible physician.

Women of childbearing potential are defined as those who are not surgically sterile (ie, underwent bilateral salpingectomytubal ligation, bilateral oophorectomy, or complete hysterectomy) or post-menopausal.

Non-sterilised male patients who intend to be sexually active with a female partner of childbearing potential must use a condom with spermicide from screening until 4 months after the last dose of study drug. It is strongly recommended for the female partners of a male patient to also use at least one highly effective method of contraception, as described in Table 3, throughout this period. In addition, male patients should refrain from fathering a child, freezing or donating sperm during the study and for 4 months after the last dose of study drug. Preservation of sperm should be considered prior to enrolment in this study.

Table 3 Highly Effective Methods of Contraception (<1% failure rate)

Non-hormonal Methods	Hormonal Methods
• Total heterosexual abstinence (evaluate in relation to the duration of the clinical study and the preferred and usual lifestyle choice of the participant) • Vasectomised sexual partner (provided that partner is the sole sexual partner of the trial participant and that the vasectomised partner has received medical assessment of the surgical success) • Bilateral tubal occlusion • Intrauterine device (provided coils are copper banded)	• Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation ◦ Oral ◦ Intravaginal ◦ Transdermal • Progestogen-only hormonal contraception associated with inhibition of ovulation ◦ Oral ◦ Injectable ◦ Implantable • Intrauterine hormone-releasing system (IUS)

5.4 Screen failures

Please refer to Section 5.4 of the core protocol.

6. STUDY TREATMENTS

Study treatment is defined as any study drug(s) (including marketed product comparator and placebo) or medical device(s) intended to be administered to a study participant according to the study protocol. Study treatment in Module 6 refers to durvalumab and trastuzumab deruxtecan.

6.1 Treatments administered

6.1.1 Study drugs

Table 4 Study drugs

Study drug name:	Trastuzumab deruxtecan (DS-8201a)	Durvalumab
Dosage formulation:	Trastuzumab deruxtecan (DS-8201a) Lyo-DP is a vialed, sterile, lyophilized drug product and is reconstituted with 5 mL of water for injection. One strength (100 mg/vial), will be provided.	Supplied as a vialed liquid solution containing 500 mg (nominal) durvalumab per vial. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine hydrochloride, 275 mM trehalose dihydrate, 0.02% (w/v) polysorbate 80, at pH 6.0. The nominal fill volume is 10.0 mL.
Route of administration	IV infusion	IV infusion
Dosing instructions: Please refer to Section 6.2 for study specific handling instructions	Trastuzumab deruxtecan (DS-8201a) 5.4 mg/kg via IV infusion Q3W +2 days	Durvalumab 1120 mg via IV infusion Q3W +2 days.
Packaging and labelling	Trastuzumab deruxtecan (DS-8201a) Lyo-DP is provided in vials. Labels will be prepared in accordance with GMP and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language, as required, and will be provided with either single-panel labels or multi-language booklet labels. The vials will be labelled 'DS-8201a' (not trastuzumab deruxtecan). The investigator's emergency contact details will not be on the label, but can be found in the informed consent and the 'Patient Emergency Card'. For emergency purposes the patient must be in possession of the emergency contact details at all times.	Study drug will be provided in vials. Each vial will be labelled in accordance with GMP and per country regulatory requirement. Labels will be prepared in accordance with GMP and local regulatory guidelines. Label text will be translated into local language, as required. Durvalumab will be provided with either single-panel labels or multi-language booklet labels. The investigator's emergency contact details will not be on the label, but can be found in the informed consent and the 'Patient Emergency Card'. For emergency purposes, the patient must be in possession of the emergency contact details at all times.

Provider	AstraZeneca. Commercially available 5% (w/v) dextrose IV bags will be supplied by each site.	AstraZeneca. Commercially available 0.9% (w/v) saline or 5% (w/v) dextrose IV bags will be supplied by each site.

BD twice daily; GMP Good Manufacturing Practice; IV intravenous(ly); Q3W every 3 weeks; w/v weight/volume

6.2 Preparation/handling/storage/accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study drugs received and any discrepancies are reported and resolved before use of the study drug.

Only patients enrolled in the study may receive study drugs and only authorised site staff may supply or administer study drugs. All study drugs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study drugs accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study drug are provided in the Pharmacy Manual.

6.2.1 Durvalumab preparation and handling

Durvalumab will be supplied by AstraZeneca as a 500 mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine hydrochloride, 275 mM trehalose dihydrate, and 0.02% weight/volume (w/v) polysorbate 80; it has a pH of 6.0 and a density of 1.054 g/mL. The nominal fill volume is 10.0 mL.

Study drug vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. The vials should be kept in the original packaging until use to prevent prolonged light exposure.

The dose of durvalumab for administration must be prepared by the investigator's or site's designated study drug manager using aseptic technique. Total time from needle puncture of the durvalumab vial to the start of administration should not exceed 4 hours at room temperature or 24 hours at 2°C to 8°C (36°F to 46°F). If the final product is stored at both refrigerated and ambient temperatures, the total time should not exceed 24 hours.

A dose of 1120 mg will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab concentration ranging from 1 to 15 mg/mL and delivered through an IV-administration set with a 0.2-µm or 0.22-µm filter. Add 22.4 mL (ie, 1120 mg) of durvalumab to an appropriately sized IV bag such that the final concentration is

within 1 to 15 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

Standard infusion time is one hour (±15 minutes), however if there are interruptions during infusion, the total allowed infusion time should not exceed 8 hours at room temperature.

If either preparation time or infusion time exceeds the time limits a new dose must be prepared from new vials. Durvalumab does not contain preservatives, and any unused portion must be discarded.

Do not co-administer other drugs through the same infusion line.

The IV line will be flushed with a volume of IV diluent equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered.

Durvalumab should be given at least 1 hour after the patient has received their trastuzumab deruxtecan infusion. Patients will be monitored before, during, and after the first durvalumab infusion with assessment of vital signs at the times specified in the SoA (Table 1) and Section 8.2.3 of the core protocol. If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be at the investigator's discretion (suggested 30 minutes after each durvalumab infusion). For management of patients who experience an infusion reaction, please refer to the toxicity and management guidelines for infusion-related reactions.

Durvalumab (1120 mg) will be administered via IV infusion Q3W +2 days. Treatment with durvalumab will commence on Day 1 following confirmation of eligibility and will continue on a Q3W schedule until disease progression is confirmed.

6.2.2 Trastuzumab deruxtecan preparation and handling

Trastuzumab deruxtecan (DS-8201a) Lyo-DP is a sterile, lyophilized drug product individually packaged in amber borosilicate (Type I) glass vials and carton, and is reconstituted with 5 mL of water for injection. One strength (100 mg/vial), will be provided. Each vial is for single use only.

Trastuzumab deruxtecan (DS-8201a) Lyo-DP must be administered IV, or in some cases via cardiovascular port. It is supplied in labelled cartons each containing 1 vial. Each vial and carton will be labelled DS-8201a (not trastuzumab deruxtecan). Vials should be stored in a secure refrigerator 2°C to 8°C and protected from light.

Please note the following:

- The outer carton box(es) must remain together with vial(s) until solution preparation is complete.
- Trastuzumab deruxtecan (DS-8201a) Lyo-DP is not compatible with saline.
- During administration, the prepared infusion bag must be covered by a light protection cover.

The infusion time for trastuzumab deruxtecan is approximately 90 minutes on Cycle 1 Day 1. If there is no infusion-related reaction, for subsequent cycles the infusion time is a minimum of 30 minutes.

The patient's weight at Screening (baseline) will be used to initially calculate the dose of trastuzumab deruxtecan. For subsequent cycles, if the patient's weight increases or decreases by ≥10%, the dose will be recalculated.

For detailed instructions on the proper usage of trastuzumab deruxtecan (DS-8201a) Lyo-DP in the clinic, please refer to the pharmacy manual.

6.2.3 Study drug administration

It is important to follow the assessment schedule as closely as possible.

Patients should continue to receive study treatment (ie, durvalumab in combination with trastuzumab deruxtecan) until objective radiological disease progression as per Response Evaluation Criteria in Solid Tumours (RECIST 1.1), as long as, in the investigator's opinion, they are benefiting from treatment and they do not meet any other discontinuation criteria. Disease progression should be confirmed by a subsequent scan (no earlier than 4 weeks later) in the absence of clinically significant deterioration as assessed by the investigator. All patients who have objective progression of disease will enter follow-up.

Table 6Trastuzumab deruxtecan is emetogenic, which includes delayed nausea and/or vomiting. Prior to each dose of trastuzumab deruxtecan, patients should be premedicated with a combination regimen of 2 or 3 medicinal products (eg, dexamethasone with either a 5-hydroxytryptamine receptor [5-HT3] antagonist and/or a Neurokinin-1 (NK1) receptor antagonist, as well as other medicinal products as indicated) for prevention of chemotherapy-induced nausea and vomiting (Table 6).

6.2.4 Storage

All study drugs should be kept in a secure place under appropriate storage conditions.

Durvalumab and trastuzumab deruxtecan are to be stored at the study centre in a secured facility with restricted access and controlled temperature (2ºC to 8ºC). The temperature

should be monitored on a daily basis and documented in the temperature monitoring log according to the study drug handling instructions. Trastuzumab deruxtecan should be protected from light.

The study drug must be kept in the original outer container and under conditions specified on the labels.

In the following cases, the centre staff should not use affected study drug and should immediately contact AstraZeneca representative for further guidance:

- Temperature excursion upon receipt or during storage at the study site
- Damaged kit upon receipt
- Damaged vial.

Damaged study drug should be documented according to the instructions provided by AstraZeneca representative. Storage conditions stated in the Investigator's Brochure, or the study drug Handling Instructions document, may be superseded by the label storage.

6.2.5 Accountability

The study drugs provided for this study should be used only as directed in the study protocol.

The study site staff will account for all study drugs received at the centre, for unused study drugs, and for appropriate destruction (according to local procedures). Certificates of delivery, destruction, and/or return should be signed.

The administration of all medications (including study drug) and details of treatment with study drug should be recorded in the appropriate sections of the electronic Case Report Form (eCRF).

6.3 Measures to minimise bias: randomisation and blinding

This is an open-label study.

Recruitment to the biomarker-matched cohorts will be based upon a predefined schema (described in the Pathology and Genomic Testing Manual) for patient allocation which takes account of biomarker prevalence estimates and the platform of evidence for each study treatment.

If a patient withdraws from participation in the study, then his/her enrolment code cannot be reused. Withdrawn patients will not be replaced.

6.4 Treatment compliance

The administration of all study drugs should be recorded in the appropriate sections of the eCRF. Durvalumab and trastuzumab deruxtecan will be administered on site. Treatment compliance will be assured by reconciliation of site drug accountability logs.

Any change from the dosing schedule, does interruptions, dose reductions, dose discontinuations should be recorded in the eCRF. Note: Dose reductions are not allowed for durvalumab (see Section 6.6).

The Study Drug Storage Manager is responsible for managing the study drug from receipt by the study site until the destruction or return of all unused study drug.

Use of study treatment in doses in excess of that specified in the protocol is considered to be an overdose. Refer to Section 8.4.3 for procedures in case of overdose.

6.5 Concomitant therapy

Any medication or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the patient is receiving at the time of enrolment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Prohibited concomitant medications are described in Table 5.

Please refer to Section 8.4.5 for guidance on management of study drug-related toxicities.

The use of concomitant medications must be recorded in the eCRF.

Table 5 Prohibited medications

Prohibited medication/class of drug:	
Unless stated otherwise, these medications are prohibited from the time that patients enter the main screening period until the last dose of study treatment. The pre-screen may be done whilst on prior therapy.	
Any investigational anticancer therapy other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment
Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment. (Note: concurrent use of hormones for non-cancer-related conditions [eg, insulin for diabetes and hormone replacement therapy] is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable [eg, by local surgery or radiotherapy]). Patients may receive treatment with bisphosphonates or RANKL inhibitors for the treatment of bone metastases. Radiotherapy to the thorax is not allowed at any time
Immunosuppressive medications, including, but not limited to: systemic corticosteroids at doses exceeding 10 mg/day of prednisone or its equivalent, methotrexate, azathioprine, and tumour necrosis factor-α blockers	Should not be given concomitantly, or used for premedication prior to the infusions. The following are allowed exceptions: • Use of immunosuppressive medications for the management of study drug-related AEs • Short-term premedication for patients receiving combinations where the prescribing information for the agent requires the use of steroids for documented hypersensitivity reactions or prophylaxis for nausea/vomiting • Use in patients with contrast allergies • In addition, use of inhaled, topical, and intranasal corticosteroids is permitted. A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of non-immunotherapy related events experienced by the patient (eg, chronic obstructive pulmonary disease, radiation, nausea, etc).
Live attenuated vaccines	Prohibited from the time that patients enter the main screening period until 180 days after the last dose of study treatment.
Epidermal growth factor receptor (EGFR) Tyrosine kinase inhibitors (TKIs)	Should not be given concomitantly. Should be used with caution in the 90 days post last dose of durvalumab. Increased incidences of pneumonitis (with third generation EGFR TKIs) and increased incidence of transaminase increases (with 1st generation EGFR TKIs) have been reported when durvalumab has been given concomitantly.
Herbal and natural remedies which may have immune-modulating effects	Should not be given concomitantly unless agreed by the sponsor
Chloroquine and hydroxychloroquine	Chloroquine and hydroxychloroquine have been shown in vitro to substantially affect the pH of the lysosome, a key intracellular compartment involved in the trafficking and payload release of trastuzumab deruxtecan. As it is unknown whether chloroquine/ hydroxychloroquine may affect the safety and efficacy of trastuzumab deruxtecan, chloroquine and hydroxychloroquine are considered prohibited concomitant medications.

AE adverse event

The use of herbal preparations/medications should be discouraged throughout the study. These herbal medications include, but are not limited to: St. John's Wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone, yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 7 days prior to first dose of study drug (3 weeks for St John's Wort). Use of these products, as well as use of all vitamins, nutritional supplements and all prescribed concomitant medications, must be recorded in the eCRF.

Other concomitant treatment

Medication other than that described above, which is considered necessary for the patient's safety and wellbeing, may be given at the discretion of the investigator and recorded in the appropriate sections of the eCRF.

6.5.1 Rescue and supportive medication

The study site will supply rescue medication and this will be procured locally. The sponsor will supply only if required by local regulations.

The use of rescue medications is allowable at any time during the study. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

Supportive medication, described in Table 6, may be given at the discretion of the investigator and recorded in the appropriate section of the eCRF.

Table 6 Supportive medication

Supportive medication/class of drug:	Usage:
Concomitant medications or treatments (eg, acetaminophen or diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care, except for those medications identified as "prohibited," as listed above	To be administered as prescribed by the investigator
Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy to non-target lesions not in the thorax, etc]).	Should be used, when necessary, for all patients
Inactivated viruses, such as those in the influenza vaccine or authorised and approved COVID-19 vaccines.	Permitted. Administration of COVID-19 vaccines should be avoided for 72 hours prior to administration of the first dose of study treatment, or during the dose-limiting toxicity period.

Table 6 Supportive medication

Supportive medication/class of drug:	Usage:
Haematopoietic growth factors may be used for prophylaxis or treatment	Based on clinical judgement of the Investigator
Antiemetics such as 5-hydroxytryptamine receptor (5-HT3) antagonists or Neurokinin-1 (NK1) receptor antagonists and/or steroids (eg dexamethasone) should be considered for prophylaxis.Table 5	Based on the currently available clinical safety data, it is recommended that patients receive prophylactic anti-emetic agents prior to infusion of trastuzumab deruxtecan and on subsequent days, and administered in accordance with the prescribing information or institutional guidelines

COVID-19 Coronavirus Disease 2019.

6.5.2 Effect of trastuzumab deruxtecan on other drugs

Nonclinical PK studies have indicated that MAAA-1181a, one of the components of trastuzumab deruxtecan, is primarily metabolised by cytochrome P450 (CYP) 3A4 and is a substrate for OATP1B1 and 1B3, MATE2-K, P-gp, BCRP, and MRP1. The data from Study DS8201-A-A104 showed that concomitant use of ritonavir (a dual inhibitor of OATP1B/CYP3A) and itraconazole (a CYP3A inhibitor) resulted in a minimal increase in the exposure of MAAA-1181a, with increases of 22% and 18% in AUC_{17d}, respectively. Results from this study indicated that these inhibitors have no clinically meaningful effect on the exposures of trastuzumab deruxtecan and MAAA-1181a. Therefore, Study DS8201-A-A104 suggested that strong CYP3A4 inhibitors (eg, boceprevir, clarithromycin, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, telaprevir, telithromycin, and voriconazole) or OATP1B inhibitors (eg, lopinavir/ritonavir, cyclosporine, and rifampicin) can be administered without trastuzumab deruxtecan dose adjustment.

6.6 Dose modification and discontinuation

The dose of durvalumab cannot be modified.

Durvalumab dosing can be interrupted in the event of treatment-related toxicity. All toxicities will be graded according to CTCAE version 4.03. Please refer to the toxicity management guidelines for durvalumab.

Prophylactic or supportive treatment for expected toxicities, including management of study drug induced AEs will be as per treating physician discretion and institutional guidelines.

Dose reductions (of trastuzumab deruxtecan only) or interruptions, and initiation of supportive care, are allowed as deemed appropriate by the treating physician. If treatment with durvalumab and/or trastuzumab deruxtecan is delayed for more than 2 days from the scheduled cycle start date, then both study medications will be delayed until the combination can be resumed at the next scheduled cycle or after the restart criteria are met for both drugs.

Any patient requiring a toxicity-related dose delay of 28 days (+2-day window) must be discontinued from the study treatment unless there is approval from the Study Physician for the patient to continue. Refer to Section 8.4.5 Management of study drug related toxicities for delay and stopping criteria for the study drugs. A patient may continue on monotherapy if the other treatment is permanently stopped (core protocol Section 7.1.1).

One initial starting dose of trastuzumab deruxtecan will be used in this study. This starting dose of trastuzumab deruxtecan Lyo-DP formulation will be 5.4 mg/kg. Two dose reductions, firstly to 4.4 mg/kg and secondly to 3.2 mg/kg, will be permitted. If the reduced dose of 3.2 mg/kg is not tolerable, no further dose reduction is allowed and study treatment should be discontinued. Once the dose is reduced, escalation is not permitted.

6.7 Treatment after the end of the study

Patients are permitted to either receive standard of care therapy, or to continue to receive study treatment following the end of the study if, in the opinion of the investigator, they are continuing to receive benefit from treatment. After discontinuation of study treatment, the investigator will be at liberty to define further most appropriate anti-cancer treatment. Subsequent anti-cancer treatment is expected to be initiated following the cancer recurrence or development of a new cancer. Information on subsequent anti-cancer therapies should be recorded on the clinical database.

7. DISCONTINUATION OF TREATMENT AND PATIENT WITHDRAWAL

Please refer to Section 7 in the core protocol.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in the SoA (Table 1).

8.1 Efficacy assessments

Please refer to the core protocol.

8.2 Safety assessments

8.2.1 Clinical safety laboratory assessments

Please refer to core protocol for standard laboratory assessments. In addition, troponin-T (preferably high-sensitivity troponin-T) should be assessed at the timepoints in Table 1. If it is not possible to assess troponin T, then sites should assess troponin I instead. All samples for a patient should be assessed using the same Troponin test at the same laboratory throughout the study where feasible.

Troponin will be measured at screening, study drug discontinuation, and if at any time a patient reports signs and symptoms suggesting congestive heart failure, myocardial infarction, or other causes of myocyte necrosis.

If troponin levels are consistent with myocardial infarction as defined according to manufacturer (CTCAE Grade 3), perform ECG testing in triplicate, repeat troponin testing 6 hours (±1 hour) and 12 hours (±1 hour) after initial troponin test was drawn, and follow institutional guidelines. If troponin levels are above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer (CTCAE Grade 1), repeat troponin testing at 3 hours (±1 hour) (~6 hours post-infusion) after initial troponin test was drawn. If repeat troponin levels at 3 hours (±1 hour) (~6 hours post-infusion) is above the upper limit of normal at baseline, below the level of myocardial infarction as defined by the manufacturer (CTCAE Grade 1), and not classified as CTCAE Grade 3, no further repeat testing is required. If repeat troponin level at 3 hours (±1 hour) (~6 hours post-infusion) rises significantly per institutional guidelines: perform ECG in triplicate; repeat troponin testing at 6 hours (±1 hour) (~9 hours post infusion) after initial troponin test; follow institutional guidelines for management of detectable troponin testing. Otherwise, repeat troponin testing at 6 hours (±1 hour) (~9 hours post-infusion) or at 24 hours (±2 hours) (~27 hours post-infusion) after initial troponin test.

8.2.1.1 Coagulation

Please refer to core protocol and to Table 1.

8.2.1.2 Other safety assessments

Pregnancy tests

Pregnancy tests will be performed on Day 1 of every cycle in Module 6 (see Table 1). See Section 8.2.1.2 in the core protocol for details of the pregnancy test.

Ophthalmologic assessments

Ophthalmologic assessments, including visual acuity testing, slit lamp examination, and fundoscopy, should be performed as per Table 1.

LVEF

Either echocardiogram or multi-gated acquisition (MUGA) scan will be performed as per Table 1; LVEF will be measured.

Pulmonary assessments

Chest CT or magnetic resonance imaging (MRI) of the chest (MRI only if agreed by Sponsor) will be performed as per Table 1. Additionally, peripheral oxygen saturation (SpO_2) will be measured at Screening, before and after infusion of trastuzumab deruxtecan on Day 1 of each Cycles 1, 2 and 3, measured at any time on Cycle 1 Day 8, Cycle 1 Day 15, and before

infusion on Day 1 of each subsequent cycle, and at the end of treatment visit and the follow-up visit.

Pulmonary function tests: Spirometry at baseline is required. Diffusion lung carbon monoxide (DLCO) should be performed at baseline if feasible, but for patients with prior severe and/or clinically significant pulmonary disorders DLCO is a requirement.

8.2.1.3 Pneumonitis (interstitial lung disease) investigation

If new or worsening pulmonary symptoms (eg, dyspnoea) or radiological abnormality suggestive of pneumonitis/ILD is observed, toxicity management as described in detail in the Dosing Modification and Toxicity Management Guidelines (see Section 8.4.5) will be applied. The results of the full diagnostic workup (including high-resolution computed tomography [HRCT], blood and sputum culture, haematological parameters, etc) will be captured in the eCRF. It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic oedema, or pulmonary haemorrhage. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of pneumonitis (ILD) should be considered and the Dosing Modification and Toxicity Management Guidelines should be followed.

An independent ILD adjudication committee and charter is responsible for reviewing all cases of potential ILD/pneumonitis. To ensure adequate and relevant independent evaluation, systematic additional data collection will be conducted for all cases that will be brought for adjudication. This additional data collection will cover a more in-depth relevant medical history (eg, smoking, radiation and pulmonary history), diagnostic evaluation, treatment and outcome of the event.

The following assessments, and additional assessments if required, will be performed to enhance the investigation and diagnosis of potential cases of pneumonitis. The results of the assessment will be collected.

- Physical examination; Signs and symptoms (cough, shortness of breath and pyrexia, etc) including auscultation for lung field will be assessed.
- SpO_2; Saturation of peripheral oxygen (SpO_2).
- Other items; When pneumonitis/ILD is suspected during study treatment, the following markers should be measured where possible:
  - ILD markers (KL-6, SP-D) and β-D-glucan
  - Tumour markers: Particular tumour markers which are related to disease progression.

8.2.2 Physical examinations

Please refer to core protocol.

8.2.3 Vital signs

Please refer to core protocol and Table 1. On Day 1 of Cycles 1, 2 and 3, vital signs will be assessed before and after infusion of trastuzumab deruxtecan and around the infusion of durvalumab according to the instructions for the durvalumab infusion in the core protocol. At subsequent cycles from Cycle 4 onwards blood pressure (BP), pulse rate, and other vital signs should be measured prior to the start of the trastuzumab deruxtecan infusion and recorded in the eCRF. Patients should be carefully monitored, and BP and other vital signs should be measured during and after trastuzumab deruxtecan and durvalumab infusions as per institution standard and as clinically indicated.

8.2.4 Electrocardiograms

Please refer to core protocol for methodology and Table 1 for timings in this module.

8.2.5 Performance status

Please refer to core protocol for methodology and Table 1 for timings in this module.

8.3 Collection of adverse events

Please refer to the core protocol.

The results from the CSP-mandated laboratory tests and vital signs will be summarised in the clinical study report (CSR). Deterioration as compared to pre-dose in protocol-mandated targeted physical examination, vital signs, and clinical safety laboratory values, should therefore only be reported as AEs if they fulfil any of the SAE criteria, are considered DLTs in the safety run-in, or are the reason for discontinuation of treatment with the study drug, or are considered to be clinically relevant as judged by the investigator (which may include but not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study treatment, eg, dose adjustment or drug interruption).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the pre-dose assessment will be reported as an AE.

All confirmed or suspected COVID-19 infection events must be recorded in the eCRF. Please refer to Section 11 for additional information on dose modification.

ILD/pneumonitis

All potential ILD cases (either serious or non-serious) should be reported to the sponsor and also in the clinical study database within 24 hours.

For ILD/pneumonitis, safety follow up will be continued until resolution of ILD/pneumonitis. If an event that starts post the defined safety follow up period is considered to be due to a late onset toxicity to study treatment, then it should be reported as an AE or SAE as applicable.

8.4 Safety reporting and medical management

8.4.1 Reporting of serious adverse events

Please refer to the core protocol.

8.4.2 Pregnancy

Please refer to the core protocol.

8.4.3 Overdose

Please refer to the core protocol.

8.4.4 Medication error

Please refer to the core protocol.

8.4.5 Management of study drug-related toxicities

At this time, there are limited safety data regarding the combination of durvalumab and trastuzumab deruxtecan. Given the differing mechanisms of action of durvalumab and trastuzumab deruxtecan, the potential for potentiation of toxicities is thought to be limited. Some known overlapping toxicities, for example ILD/pneumonitis, diarrhoea/colitis, and infusion-related reactions may, on theoretical grounds, be potentiated in the combination arm and particular attention should be paid to these.

In the event of toxicity in this combination arm of the study which cannot be managed by supportive measures alone, stopping one or both medications should be an investigator decision based on the available information and, if necessary, following discussion with the sponsor.

The following general guidance should be followed for management of toxicities:

- If any toxicity is judged by the treating physician to be related to both durvalumab AND trastuzumab deruxtecan then the most conservative toxicity management (comparing

durvalumab and trastuzumab deruxtecan toxicity management guidelines) should be adopted. Specifically, for the following toxicities where both study drugs are causally implicated the following guidelines should be followed:

  - Decreased LVEF: durvalumab toxicity management
  - QTc prolongation: durvalumab toxicity management
  - Hepatic toxicity: durvalumab toxicity management
  - Haematological toxicity: durvalumab toxicity management
  - Infusion-related reactions: trastuzumab deruxtecan toxicity management
  - Pulmonary toxicity (pneumonitis/ILD): trastuzumab deruxtecan toxicity management.

- Treat each of the toxicities with maximum supportive care (including withholding the agent suspected of causing the toxicity if required).
- If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of the assigned study drug along with continuing supportive care, where appropriate. If medically appropriate, dose modifications are permitted for trastuzumab deruxtecan. In addition, guidelines on trastuzumab deruxtecan dose modifications are provided in Section 6.6. In the event of toxicity that cannot be managed by following the toxicity management guidelines for trastuzumab deruxtecan and durvalumab, consider stopping treatment with trastuzumab deruxtecan.

All dose modifications should be documented with clear reasoning and documentation of the approach taken. Dose reductions are not permitted without prior agreement with the study physician.

8.4.5.1 Management of durvalumab-related toxicities

Please refer to the toxicity management guidelines for durvalumab.

8.4.5.2 Management of trastuzumab deruxtecan-related toxicities

All dose modifications (interruption, reduction and/or discontinuation) (Section 6.6) should be based on the worst preceding toxicity. Specific criteria for interruption, re-initiation, dose reduction and/or discontinuation of trastuzumab deruxtecan are listed in Table 7 below, which is applicable only to TEAEs that are assessed as related to use of trastuzumab deruxtecan by the investigator. For non-drug related TEAEs, follow standard clinical practice. Appropriate clinical experts should be consulted as deemed necessary.

If AE causality is possibly, probably or definitely related to both durvalumab and trastuzumab deruxtecan, the most conservative toxicity guidance (either durvalumab or trastuzumab deruxtecan) should be adopted. Discussion with the sponsor's medical monitor is recommended in such cases.

Further guidance on ILD/pneumonitis management and LVEF management are provided in Sections 8.4.5.3 and 8.4.5.4.

Table 7 Toxicity management guidelines for trastuzumab deruxtecan

Worst toxicity CTCAE v4.03 Grade (unless otherwise specified)	**Management guidelines for trastuzumab deruxtecan**
No toxicity	Maintain dose and schedule
Infusion-related reaction	
Grade 1 (Mild transient reaction; infusion interruption not indicated; intervention not indicated)	If infusion related reaction (such as fever and chills, with and without nausea/vomiting, pain, headache, dizziness, dyspnoea, hypotension) is observed during administration, the infusion rate should be reduced by 50% and subjects should be closely monitored. If no other reactions appear, the subsequent infusion rate could be resumed at the initial planned rate.
Grade 2 (Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, nonsteroidal anti-inflammatory drugs (NSAIDs), narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs)	Administration of trastuzumab deruxtecan should be interrupted and symptomatic treatment started (eg, antihistamines, NSAIDs, narcotics, IV fluids). If the event resolves or improves to Grade 1, infusion can be restarted at a 50% reduced infusion rate. Subsequent administrations should be conducted at the reduced rate.
Grade 3 or 4 (Prolonged or life-threatening consequences, urgent intervention indicated)	Administration of trastuzumab deruxtecan should be discontinued immediately and permanently. Urgent intervention indicated. Antihistamines, steroids, epinephrine, bronchodilators, vasopressors, intravenous fluid therapy, oxygen inhalation etc, should be administered.
Haematologic toxicity (if supportive therapy fails [as clinically indicated and according to local practice], consider additional TMGs as below) Note: Trastuzumab deruxtecan should be permanently discontinued if any Grade 4 trastuzumab deruxtecan-related haematological toxicity with significant clinical symptoms that do not resolve with treatment within 4 weeks occurs. Resuming the study drug will be possible if the toxicity resolves, and in consultation with the study physician.	
Neutrophil count decreased and/or white blood cell count decreased	
Grade 3	Delay dose until resolved to ≤Grade 2, then maintain dose
Grade 4	Delay dose until resolved to ≤Grade 2, Reduce dose 1 level
Febrile neutropenia (absolute neutrophil count <1 x 10^9/L, fever >38.3°C or a sustained temperature of ≥38 °C for more than 1 hour)	Delay dose until resolved, Reduce dose by 1 level
Lymphocyte count decreased	
Grade 1 to Grade 3 lymphopenia	No dose modification

Table 7 Toxicity management guidelines for trastuzumab deruxtecan

Worst toxicity CTCAE v4.03 Grade (unless otherwise specified)	Management guidelines for trastuzumab deruxtecan
Grade 4 (<0.2 x 10^9/L)	Delay dose until resolved to ≤Grade 2: • If resolved in ≤14 days from day of onset, maintain dose • If resolved in >14 days from day of onset, reduce dose 1 level
Anaemia	
Grade 3 (Haemoglobin <8.0 g/dL); transfusion indicated	Delay dose until resolved to ≤Grade 2, then maintain dose
Grade 4 Life threatening consequences; urgent intervention indicated	Delay dose until resolved to ≤Grade 2, then reduce dose 1 level
Platelet count decreased	
Grade 3 (platelets <50 – 25 x 10^9/L)	Delay dose until resolved to ≤Grade 1: • If resolved in ≤7 days from day of onset, maintain dose • If resolved in >7 days from day of onset, reduce dose 1 level
Grade 4 (platelets <25 x 10^9/L)	Delay dose until resolved to ≤Grade 1, then reduce dose 1 level
Cardiac toxicity (see also Section 8.4.5.4)	
Symptomatic CHF	Discontinue subject from study treatment
Grade 2: Decrease in LVEF 10% to 20% (absolute value), but LVEF >45%	Continue treatment with trastuzumab deruxtecan
Grade 2: LVEF 40% to ≤45% and decrease is <10% (absolute value) from baseline	Continue treatment with trastuzumab deruxtecan Repeat LVEF assessment within 3 weeks
Grade 2: LVEF 40% to ≤45% and decrease is 10% to 20% (absolute value) from baseline	Interrupt trastuzumab deruxtecan dosing Repeat LVEF assessment within 3 weeks. If LVEF has not recovered to within 10% (absolute value) from baseline, discontinue patient from study treatment If LVEF recovers to within 10% from baseline, resume study drug treatment
Grade 3: LVEF <40% or >20% (absolute value) drop from baseline	Interrupt trastuzumab deruxtecan dosing. Repeat LVEF assessment within 3 weeks. If LVEF <40% or >20% drop from baseline is confirmed, discontinue subject from study treatment. IF LVEF has recovered to > 40% and decrease is < 20% from baseline, follow appropriate guidance above.

Table 7 Toxicity management guidelines for trastuzumab deruxtecan

Worst toxicity CTCAE v4.03 Grade (unless otherwise specified)	Management guidelines for trastuzumab deruxtecan
QTc Prolongation	
Grade 3 (Average QTc >500 ms or >60 ms change from baseline)	Delay dose until resolved to ≤Grade 1 (corrected QT ≤480 ms), determine if another medication the patient was taking may be responsible and can be adjusted or if there are any changes in serum electrolytes that can be corrected, then if attributed to trastuzumab deruxtecan, reduce dose 1 level
Grade 4 (Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia)	Discontinue subject from study treatment
Pulmonary Toxicity (see also Section 8.4.5.3)	Work-up of suspected ILD/pneumonitis: If a subject develops radiographic changes potentially consistent with ILD/pneumonitis or develops an acute onset of new or worsening pulmonary or other related signs/symptoms such as dyspnoea, cough or fever, rule out ILD/pneumonitis. Evaluations should include: • high resolution CT • pulmonologist consultation (infectious disease consultation as clinically indicated) • Blood culture and complete blood count. Other blood tests could be considered as needed • Consider bronchoscopy and bronchoalveolar lavage if clinically indicated and feasible • pulmonary function tests and pulse oximetry (SpO_2) • arterial blood gases if clinically indicated • one blood sample collection for PK and exploratory biomarker analysis as soon as ILD is suspected, if feasible. Other tests could be considered, as needed. If the AE is confirmed to have an aetiology other than treatment-related ILD/pneumonitis, follow the management guidance outlined in the "Other Non-Laboratory Adverse Events" dose modifications. If another aetiology for the AE cannot be identified and it could be related to trastuzumab deruxtecan, then follow the ILD/pneumonitis management guidance as outlined below. All events of ILD regardless of severity or seriousness will be followed until resolution.

Table 7 Toxicity management guidelines for trastuzumab deruxtecan

Worst toxicity CTCAE v4.03 Grade (unless otherwise specified)	Management guidelines for trastuzumab deruxtecan
Grade 1	Management: • Monitor and closely follow-up in 2 to 7 days for onset of clinical symptoms and pulse oximetry then weekly as indicated. • Consider follow-up imaging in 1-2 weeks (or as clinically indicated). • Consider starting systemic steroids (eg, at least 0.5 mg/kg/day prednisone or equivalent) until improvement, followed by gradual taper over at least 4 weeks. • If worsening of diagnostic observations despite initiation of corticosteroids, then follow Grade 2 guidelines.* Dose modification: The administration of trastuzumab deruxtecan must be interrupted. Trastuzumab deruxtecan can be restarted only if the event is fully resolved to Grade 0: • If resolved in ≤28 days from day of onset, maintain dose • If resolved in >28 days from day of onset, reduce dose 1 level However, if the event Grade 1 ILD/pneumonitis has not resolved within 18 weeks (126 days) from the last infusion, the drug should be discontinued. * If a subject is asymptomatic, then the subject should still be considered as Grade 1 even if steroid treatment is given
Grade 2	Dose Modification: Permanently discontinue subject from study treatment. Management: • Promptly start and treat with systemic steroids (eg, at least 1 mg/kg/day prednisone or equivalent) for at least 14 days followed by a gradual taper over at least 4 weeks. • Monitor symptoms closely. • Re-image as clinically indicated. • If worsening or no improvement in clinical or diagnostic observations in 3-5 days, ° Consider increasing dose of steroids (eg, 2 mg/kg/day prednisone or equivalent) and administration may be switched to intravenous (eg, methylprednisolone). ° Re-consider additional work-up for alternative aetiologies as described above. ° Escalate care as clinically indicated.

Table 7 Toxicity management guidelines for trastuzumab deruxtecan

Worst toxicity CTCAE v4.03 Grade (unless otherwise specified)	Management guidelines for trastuzumab deruxtecan
Grade 3 or 4	Dose modification: Permanently discontinue subject from study treatment. Management: • Hospitalisation required. • Promptly initiate empiric high-dose methylprednisolone IV treatment (eg, 500-1000 mg/day for 3 days), followed by at least 1.0 mg/kg/day of prednisone (or equivalent) for at least 14 days, followed by a gradual taper over at least 4 weeks. • Re-image as clinically indicated. • If still no improvement within 3 to 5 days, ° Re-consider additional work-up for alternative aetiologies as described above. ° Consider other immunosuppressants and/or treat per local practice.
Ocular	
Grade 3	Delay dose until resolved to ≤Grade 1: • If resolved in ≤7 days from day of onset, maintain dose • If resolved in >7 days from day of onset, reduce dose 1 level
Grade 4	Discontinue subject from study treatment
Blood creatinine increased	
Grade 3 (>3.0 to 6.0 x ULN)	Delay dose until resolved to ≤Grade 2 or baseline, then reduce dose 1 level
Grade 4 (>6.0 x ULN)	Discontinue subject from study treatment
Hepatic toxicity	
Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) with simultaneous blood bilirubin increased	
AST/ALT ≥3.0 x ULN with simultaneous total bilirubin ≥2.0 x ULN	Delay study medication until drug-induced liver injury can be ruled out. If drug-induced liver injury is ruled out, the subject should be treated accordingly, and resumption of study drug may occur after discussion between the Investigator and Sponsor. If drug-induced liver injury cannot be ruled out from diagnostic workup, permanently discontinue study treatment. Monitor AST/ALT and total bilirubin twice weekly until resolution or return to baseline.
AST or ALT	
Grade 2 (>3.0 - 5.0 x ULN if baseline was normal; >3.0 to 5.0 x baseline if baseline was abnormal)	No action for Grade 2 AST/ALT

Table 7 Toxicity management guidelines for trastuzumab deruxtecan

Worst toxicity CTCAE v4.03 Grade (unless otherwise specified)	Management guidelines for trastuzumab deruxtecan
Grade 3 (>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal) In subjects without liver metastases and subjects with liver metastases and baseline level ≤3 x ULN	Repeat testing within 3 days. Delay dose until resolved to ≤Grade 1, if baseline ≤ 3 x ULN, otherwise delay dose until resolved to ≤ baseline, then: • If resolved in ≤7 days from day of onset, maintain dose • If resolved in >7 days from day of onset, reduce dose 1 level
Grade 3: (>8.0 - 20.0 x ULN if baseline was normal; >8.0 - 20.0 x baseline if baseline was abnormal) In subjects with liver metastases, if the baseline level was >3 x ULN	Repeat testing within 3 days. Delay dose until resolved to ≤ baseline level, then: • If resolved in ≤7 days from day of onset, maintain dose • If resolved in >7 days from day of onset, reduce dose 1 level
Grade 4 (>20 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal)	Discontinue subject from study treatment
Blood bilirubin increased	
Grade 2 (>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal)	If no documented Gilbert's syndrome or liver metastases at baseline, delay dose until resolved to ≤ Grade 1: • If resolved in ≤7 days from day of onset, maintain dose • If resolved in >7 days from day of onset, reduce dose 1 level If documented Gilbert's syndrome or liver metastases at baseline, continue study treatment
Grade 3 (>3.0 – 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal)	If no documented Gilbert's syndrome or liver metastases at baseline, repeat testing within 3 days. Delay dose until resolved to ≤Grade 1: • If resolved in ≤7 days from day of onset, reduce dose 1 level • If resolved in >7 days from day of onset, discontinue trastuzumab deruxtecan If documented Gilbert's syndrome or liver metastases at baseline, repeat testing within 3 days. Delay dose until resolved to ≤Grade 2: • If resolved in ≤7 days from day of onset, reduce dose 1 level • If resolved in >7 days from day of onset, discontinue trastuzumab deruxtecan
Grade 4 (>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal)	Discontinue subject from study treatment

Table 7 Toxicity management guidelines for trastuzumab deruxtecan

Worst toxicity CTCAE v4.03 Grade (unless otherwise specified)	Management guidelines for trastuzumab deruxtecan
Blood alkaline phosphatase increased	
Grade 3 (>5.0 – 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal) Or Grade 4 (>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal)	No modification unless determined by the Investigator to be clinically significant or life-threatening.
Gastrointestinal	
Nausea	
Grade 3	Delay dose until resolved to ≤Grade 1: • If resolved in ≤7 days from day of onset, maintain dose • If resolved in >7 days from day of onset, reduce dose 1 level
Diarrhoea/Colitis	
Grade 3	Delay dose until resolved to ≤Grade 1: • If resolved in ≤3 days from day of onset, maintain dose • If resolved in >3 days from day of onset, reduce dose 1 level
Grade 4	Discontinue subject from study treatment
Other laboratory adverse events	
Grade 3	Delay dose until resolved to ≤Grade 1 or baseline level: • If resolved in ≤7 days from day of onset, maintain dose • If resolved in >7 days from day of onset, reduce dose 1 level
Grade 4	Discontinue subject from study treatment
Other non-laboratory adverse events	
Grade 3	Delay dose until resolved to ≤Grade 1 or baseline: • If resolved in ≤7 days from day of onset, maintain dose • If resolved in >7 days from day of onset, reduce dose 1 level
Grade 4	Discontinue subject from study treatment

All dose modifications should be based on the worst preceding toxicity.
CTCAE: Common Terminology Criteria for Adverse Events

8.4.5.3 ILD management guidance

ILD should be ruled out if a subject develops an acute onset of new or worsening pulmonary or other related signs/symptoms such as dyspnoea, cough or fever. If the AE is confirmed to have an aetiology other than ILD, follow the management guidance outlined in the designated "Other Non-Laboratory Adverse Events" dose modification section of the study protocol.

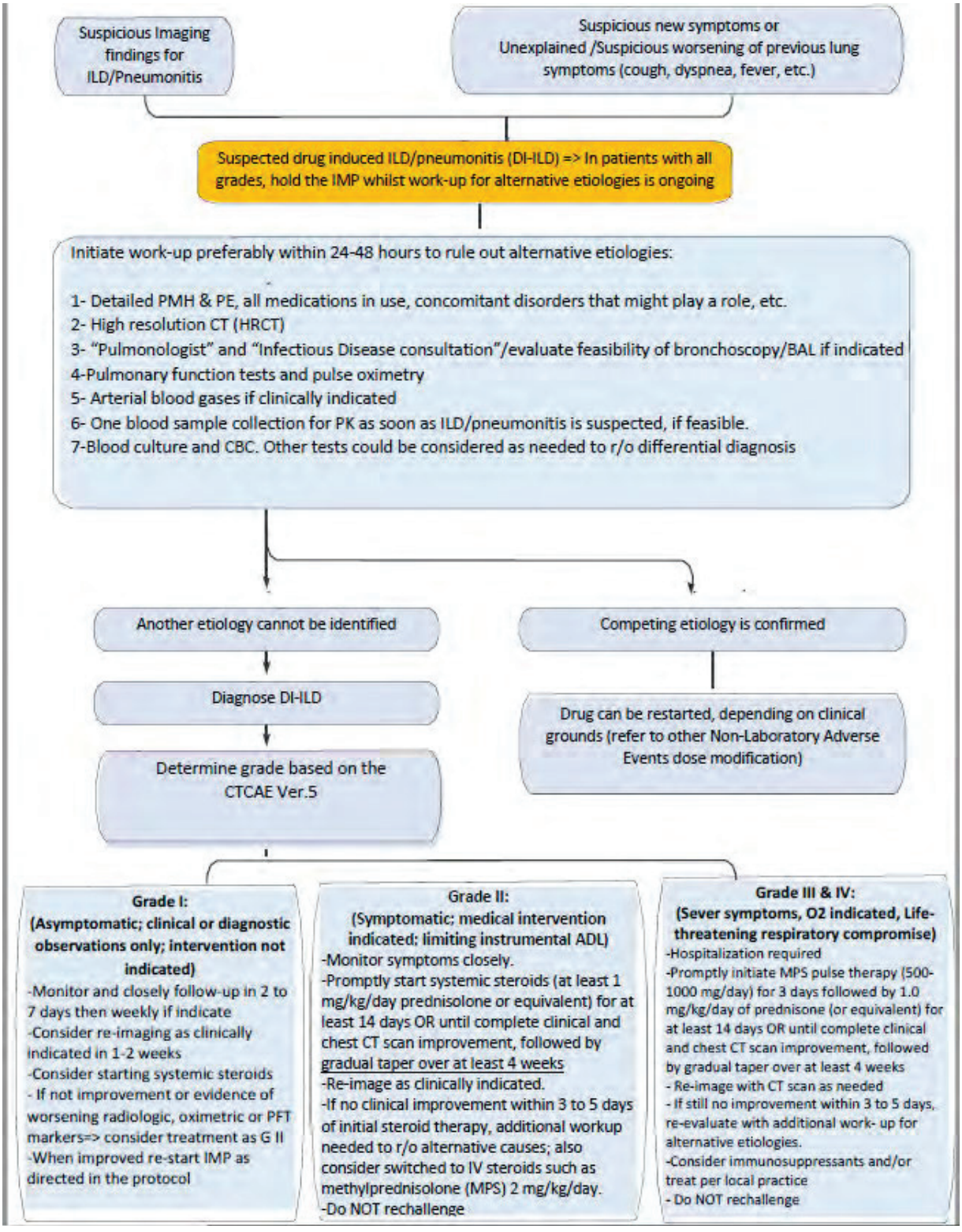
If the AE is suspected to be ILD, treatment with study drug should be interrupted pending further evaluations. Evaluations should include high resolution CT, pulmonologist consultation, pulmonary function tests and SpO_2, arterial blood gases if clinically indicated, and one blood sample collection for PK as soon as ILD is suspected, if feasible. Other tests could be considered, as needed. As soon as ILD is suspected, corticosteroid treatment should be started promptly as per clinical treatment guidelines (ILD TMGs).

An independent ILD adjudication committee and charter is responsible for reviewing all cases of potential ILD/pneumonitis. To ensure adequate and relevant independent evaluation, systematic additional data collection will be conducted for all cases that will be brought for adjudication. This additional data collection will cover a more in-depth relevant medical history (eg, smoking, radiation and pulmonary history), diagnostic evaluation, treatment and outcome of the event.

If the AE is confirmed to be ILD, follow the management guidance outlined in the designated "Pulmonary Toxicity" dose modification section of Table 7. The summary flow chart for management of drug-induced ILD is also available in Figure 3. All events of ILD regardless of severity or seriousness will be followed until resolution including after drug discontinuation.

All cases of potential ILD will be reviewed internally by medical monitor and study safety physician. Safety knowledge groups will also be consulted if needed. To ensure adequate and relevant evaluation, systematic additional data collection will be conducted for all cases that will be brought for evaluation. This additional data collection will cover a more in-depth relevant medical history (eg, smoking, radiation, COPD and other chronic lung conditions), diagnostic evaluation, treatment and outcome of the event. This data collection will be triggered for adverse events reported using 42 selected preferred terms (all from the current ILD Standard MedDRA Query) plus 2 preferred terms of acute respiratory failure and respiratory failure.

Figure 3 Drug-induced ILD/pneumonitis management flow chart



Note, CTCAE v4.03 is used in this study

8.4.5.4 LVEF management guidance

LVEF will be measured by either ECHO or MUGA scan. All ECHOs/MUGAs will be evaluated by the Investigator or delegated physician for monitoring cardiac function. The same method of assessment for a patient should be used throughout the study where feasible.

Troponin-T will be measured at screening, study drug discontinuation, and as needed based on patient reported cardiac signs or symptoms suggesting congestive heart failure, myocardial infarction, or other causes of cardiac myocyte necrosis. If it is not possible to assess troponin T, then sites should assess troponin I instead. All samples for a patient should be assessed using the same Troponin test at the same laboratory throughout the study where feasible. If 12-lead ECG is abnormal, follow institutional guidelines.

ECGs will be performed and standard ECG parameters will be measured, including RR, PR, QT intervals, and QRS duration. All ECGs must be evaluated by Investigator or delegated physician for the presence of abnormalities prior to the injection of IMP at each cycle. Whether or not measurement is performed, date performed, results, and findings for each parameter is to be recorded in the eCRF.

8.4.6 Adverse events of special interest

Adverse events of special interest (AESIs) are events of scientific and medical interest specific to understanding of the study drug and may require close monitoring and rapid communication to AstraZeneca by the investigator. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterise and understand them in association with the use of this study drug.

The AESIs for durvalumab are summarized in core protocol Section 8.3.12.

The AESIs for trastuzumab deruxtecan are ILD/pneumonitis and LVEF decrease.

A questionnaire will be sent to any investigator reporting an AESI, as an aid to provide further detailed information on the event. During the study, there may be other events identified as AESIs that require the use of a questionnaire to help characterise the event and gain a better understanding regarding the relationship between the event and study treatment.

8.5 Pharmacokinetics

Please refer to the core protocol and Table 1.

8.6 Pharmacodynamics

Pharmacodynamic parameters will be evaluated in this study (see Section 8.6 of the core protocol).

8.7 Genetics

Please refer to the core protocol.

8.8 Biomarkers

Please refer to the core protocol for information on biomarkers that apply to all modules.

Blood samples to perform exploratory safety or clinical benefit analyses to identify candidate markers which may correlate with likelihood of clinical benefit/tolerability will be collected from patients as described in the SoAs (see Section 1.1). These analyses may include but are not limited to the characterisation of the safety profile for patients with antibodies to the SARS-CoV-2 virus treated with trastuzumab deruxtecan compared to the safety profile of patients without evidence of immune response (antibodies) treated with trastuzumab deruxtecan. The presence of viruses such as the SARS-CoV-2 virus may also be investigated.

- Blood samples for plasma and serum isolation will be collected from all patients as per Table 1.

Details on sample collection, processing, handling, shipment, and storage are provided in the Laboratory Manual.

8.9 Medical Resource Utilisation and Health Economics

Health Economics/Medical Resource Utilisation and Health Economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

Please refer to the core protocol for statistical analyses relating to Cohort A.6.HER2e. Analyses for Cohort A.6.HER2m will be dependent on the number of patients recruited; details will be provided in the SAP.

Alternative tests under evaluation for HER2 expression may be deployed for retrospective evaluation of this cohort and this may require additional patients to be enrolled in this module in order to meet the approximately 20 evaluable patients as assessed using the alternative test. The alternative test is intended to be deployed prospectively if the cohort is expanded. Details will be provided in the SAP as applicable.

10. REFERENCES

Abou-Alfa et al 2006
Abou-Alfa GK, Letourneau R, Harker G, Modiano M, Hurwitz H, Tchekmedyian NS et al. Randomized phase III study of exatecan and gemcitabine compared with gemcitabine alone in untreated advanced pancreatic cancer. J Clin Oncol. 2006;24(27):4441-7.

Cheverton et al 2004
Cheverton P, Friess H, Andras C, Salek T, Geddes C, Bodoky G et al. Phase III results of exatecan (DX-8951f) versus gemcitabine (Gem) in chemotherapy-naive patients with advanced pancreatic cancer (APC). J Clin Oncol. 2004;22(14 suppl):abstr 4005.

De Jager et al 2000
De Jager R, Cheverton P, Tamanoi K, Coyle J, Ducharme M, Sakamoto N et al. DX-8951f: summary of phase I clinical trials. Ann N Y Acad Sci. 2000;922:260-73.

Garassino et al 2017
Garassino M, Vansteenkiste J, Joo-Hang K, Hervé L, Mazières J, Powderly J et al. Durvalumab in ≥3rd-line locally advanced or metastatic, EGFR/ALK wild-type NSCLC: results from the phase 2 ATLANTIC Study. J Thor Onc. 2017;12:S10-S11.

Juergens et al 2017
Juergens R, Hao D, Laurie S, Ellis P, Mates M, Bradbury P et al. Durvalumab ± tremelimumab with platinum-doublets in non-small cell lung cancer: Canadian Cancer Trials Group Study IND.226. J Thorac Onc. 2017;12(11)Suppl 2 S1839.

Li et al 2018
Li BT, Shen R, Buonocore D, Olah ZT, Ni A, Ginsberg MS et al. Ado-trastuzumab emtansine in patients with HER2 mutant lung cancers: Results from a phase II basket trial. J Clin Oncol. 2018;36(24):2532-7.

Narwal et al 2013
Narwal R, Roskos LK, Robbie GJ. Population pharmacokinetics of sifalimumab, an investigational anti-interferon alpha monoclonal antibody, in systemic lupus erythematosus. Clin Pharmacokinet. 2013;52(11):1017–27.

Ng et al 2006
Ng CM, Lum BL, Gimenez V, Kelsey S, Allison D. Rationale for fixed dosing of pertuzumab in cancer patients based on population pharmacokinetic analysis. Pharm Res. 2006;23(6):1275–84.

Stinchcombe et al 2017
Stinchcombe T, Stahel RA, Bubendorf L, Bonomi P, Villegas AE, Kowalski D et al. Efficacy, safety, and biomarker results of trastuzumab emtansine (T-DM1) in patients (pts) with

previously treated HER2-overexpressing locally advanced or metastatic non-small cell lung cancer (mNSCLC). J Clin Oncol. 2017; 35(15 Suppl):abstract 8509.

Wang et al 2009
Wang DD, Zhang S, Zhao H, Men AY, Parivar K. Fixed dosing versus body size based dosing of monoclonal antibodies in adult clinical trials. J Clin Pharmacol. 2009;49(9):1012–24.

Zhang et al 2012
Zhang S, Shi R, Li C, Parivar K, Wang DD. Fixed dosing versus body size-based dosing of therapeutic peptides and proteins in adults. J Clin Pharmacol. 2012;52(1):18–28.

11. INSTRUCTIONS RELATED TO COVID-19

Benefit Risk Considerations for COVID-19

The emergence of the coronavirus 2019-nCoV (COVID-19) presents a potential safety risk for patients. Several risk mitigation factors have been implemented in this study. Notably, the eligibility criteria will exclude participants with COVID-19 infections (see Section 5.2).

Moreover, with the outbreak of COVID-19, there is the potential for increased use of chloroquine and hydroxychloroquine to treat severely symptomatic patients, or even for prophylactic use. Chloroquine and hydroxychloroquine have been shown in vitro to substantially affect the pH of the lysosome, a key intracellular compartment involved in the trafficking and payload release of trastuzumab deruxtecan. As it is unknown whether chloroquine/hydroxychloroquine may affect the safety and efficacy of trastuzumab deruxtecan, to be eligible for this clinical study, use of chloroquine and hydroxychloroquine treatment must be completed >14 days prior to the first dose of trastuzumab deruxtecan (see Section 5.1). During study treatment, chloroquine and hydroxychloroquine are considered prohibited concomitant medications. However, in case treatment with chloroquine or hydroxychloroquine treatment is absolutely required for COVID-19, study treatment must be interrupted. After chloroquine or hydroxychloroquine is administered for COVID-19, then a wash-out period of at least 14 days is required before restarting study treatment. Additional PK samples will be taken at the following timepoints during the chloroquine/ hydroxychloroquine treatment period: Before the first dose of chloroquine/ hydroxychloroquine dosing, before chloroquine/hydroxychloroquine dosing on Day 3 or 4, on the last day of chloroquine/hydroxychloroquine treatment, pre-dose on the day of restarting trastuzumab deruxtecan treatment, if trastuzumab deruxtecan is restarted. Following these blood PK draws, if trastuzumab deruxtecan is restarted, routine trastuzumab deruxtecan PK blood sample collection will continue as per Table 1.

Lastly, due to the potential overlapping impact of trastuzumab deruxtecan and COVID-19 on the lung, the Sponsor has also provided in this Appendix, a dose modification and management plan for patients with confirmed or suspected COVID-19 who are being treated with trastuzumab deruxtecan.

With these measures in place, it is considered the anticipated potential benefits for the patients enrolled in this study outweigh the potential risks.

Inclusion criteria

1. Has adequate treatment washout period before randomisation/enrolment, defined as:
    - Chloroquine/Hydroxychloroquine: >14 days

Prior and Concomitant Medications

Concomitant treatment with chloroquine or hydroxychloroquine is not allowed during the study treatment. If treatment with chloroquine or hydroxychloroquine treatment is absolutely required for COVID-19, study treatment must be interrupted. If chloroquine or hydroxychloroquine is administered, then a wash-out period of at least 14 days is required before restarting study treatment.

Dose modification criteria

All confirmed or suspected COVID-19 infection events must be recorded in the eCRF. Dose modifications will be based on the worst CTCAE grade. All interruptions or modifications must be recorded on the AE and drug administration eCRFs. Please use CTCAE v4.03 general grading criteria to evaluate COVID-19.

Dose modification criteria for suspected or confirmed COVID-19

If COVID-19 infection is suspected, delay trastuzumab deruxtecan and rule out COVID-19 per local guidance.

- If COVID-19 is ruled out, follow study protocol.
- If COVID-19 is confirmed or diagnosis is suspected after evaluation, manage COVID-19 per local guidance until recovery of COVID-19 defined as: no signs/symptoms, at least 1 negative RT-PCR test result*, and nearly or completely resolved chest CT findings. Then follow below dose modifications:
    - If Grade 1, resume trastuzumab deruxtecan at the same dose.
    - If Grade 2
        - Maintain same dose if chest CT findings are completely resolved.
        - Reduce dose 1 level if chest CT findings are nearly resolved.
    - If Grade 3
        - Reduce dose 1 level if chest CT findings are completely resolved.

- Otherwise, discontinue study treatment.

– If Grade 4, discontinue study treatment.

Closely monitor signs/symptoms after restarting trastuzumab deruxtecan, initially with a phone call every 3 days for the first week, and then with a weekly phone call thereafter, for a total of 6 weeks.

- If an event is suspected to be drug-related ILD/pneumonitis, manage per protocol ILD/pneumonitis management guideline (Table 7).

* If PCR testing is not available, the patient must not have any sign/symptoms for at least 2 weeks, in addition to meeting the requirement for chest CT imaging.

Clinical Study Protocol	
Drug Substance	Umbrella study
Study Code	D6185C00001 (HUDSON)
Version	14.0
Date	09 October 2024

Appendix O

Module 7: Durvalumab plus cediranib (AZD2171)

An Open-Label, Multi-Drug, Biomarker-Directed, Multi-Centre Phase II Umbrella Study in Patients with Non-Small Cell Lung Cancer, who Progressed on an Anti-PD-1/PD-L1 Containing Therapy (HUDSON)

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

Regulatory Agency Identification Numbers:

EudraCT number: 2017-002208-28

EU CT number: 2023-509004-15-00

IND number: 138050

VERSION HISTORY

Version 14.0, 09 October 2024
Key amendments and rationale for changes: The version number of this module has been revised in line with the other modules in the HUDSON study; however, no changes have been made to this module.

Version 13.0, 14 December 2023
Key amendments and rationale for changes: **Front page:** EU CT number has been added in line with the core CSP.

Version 12.0, 01 March 2023
Key amendments and rationale for changes: **Section 6.2, preparation/handling/storage/accountability:** Added a reference to the Pharmacy Manual.

Version 11.0, 16 August 2022
Key amendments and rationale for changes: The version number of this module has been revised in line with the other modules in the HUDSON study; however, no changes have been made to this module.

Version 10.0, 12 April 2022
Key amendments and rationale for changes: **Table 1, schedule of activities:** Addition of footnote to clarify the activities for patients continuing on study treatment after the data cut-off for the module clinical study report.

Figure 1, study design: Addition of footnote to clarify survival follow-up of screen failures is no longer required as of protocol v10.0.

Section 2.2, background: Reference to approval of durvalumab for the treatment of urothelial carcinoma in the US removed due to voluntary withdrawal of this indication in this country. Text also added to clarify the weight-based regimen (10 mg/kg every 2 weeks) is approved for urothelial carcinoma.

Section 2.2.1.2, durvalumab data: Number of patients treated with durvalumab updated to align with durvalumab IB Edition 17.

Section 5.3.1, restrictions applicable to durvalumab; Table 4, supportive medication: Text added to provide guidance for the use and timing of authorised and approved COVID-19 vaccines, to align with the COVID-19 vaccination guidance letter (dated 24 February 2021) provided to sites.

Section 8.6, pharmacodynamics: Text updated to clarify pharmacodynamic parameters will be evaluated in the study and a cross reference to Section 8.6 of the core protocol added.

Version 9.0, 14 May 2021

Key amendments and rationale for changes:

The version number of this module has been revised in line with the other modules in the HUDSON study; however, no changes have been made to this module.

Version 8.0, 11 September 2020

Key amendments and rationale for changes:

Removal of web link to the durvalumab toxicity management guidelines as this website has been decommissioned. The toxicity management guidelines will instead be provided to sites: Section 6.2.1, Section 6.6, Section 8.4.5.1, and Table 8.

Schedule of Activities (Table 1):

- Update to the table: Number of samples for ctDNA assessment reduced after Week 24 to once every 3 cycles rather than once every cycle. To reduce the sampling burden on patients.

Section 6.2.2 (Cediranib administration): Clarification of the cediranib dose reduction schedule.

Section 6.2.3 (Study drug administration): Clarification that cediranib dosing must remain aligned to the durvalumab dosing on Day 1 of each cycle. Change also made in Section 8.4.5.2.

Section 8.2.3 (Vital signs): Clarifications on how long patients need to check their BP twice daily, and patients should contact their physician if they experience symptoms of high blood pressure. Clarifications around the responsibilities of Sponsor and Investigator. Changes also made in Section 8.4.5.2.

Section 8.4.3 (Overdose): Clarification on what constitutes an overdose of cediranib, and where this should be reported.

Section 8.4.5.2 (Management of cediranib-related toxicities): Clarification that, if patient has combined systolic (> 160 mm Hg) and diastolic (> 100 mm Hg) hypertension for > 7 days in a row, which is new in onset (subject not known previously to have hypertension) or not controlled by optimising the subject's baseline anti-hypertensive regimen (for subjects with known hypertension), a dose reduction will need to be applied. Consequential change made to Section 8.2.3 (Vital signs).

Version 7.0, 21 May 2020

Key amendments and rationale for changes:

Table 1 Schedule of Assessments:

- Cediranib dosing row merged to make it clear that dosing is 5 days on, 2 days off each week, and not only at certain visits.
- Footnote c: Updated to specify that the same ECHO/MUGA test must be used for the subject throughout the study.
- Footnote e (new): Added to state that at Main Screening, Cycle 1 Day 1, Cycle 1 Day 15, Day 1 of each subsequent cycle, and drug discontinuation, for proteinuria assessment follow instructions in Table 9.
- Footnote f (new): Added to clarify cediranib dosing in relation to durvalumab dosing.

Section 2.2 Background: Update to the registered use and approvals for durvalumab.

Section 2.2.2 Cediranib data: Updated to align with the cediranib IB Edition 22.

Figure 2 (study flow diagram): This figure has been removed from all modules and a cross reference added to the same figure in the core protocol instead. Change made to limit the number of modules requiring updating during a protocol amendment whenever a new module is added.

Section 6.2.1 Durvalumab preparation and handling: Clarification that if the final product is stored at both refrigerated and ambient temperatures, the total time should not exceed 24 hours.

Section 6.4 Treatment compliance and **Section 6.6 Dose modification and discontinuation:** Clarification that dose reductions for durvalumab are not permitted.

Section 8.2.1 Laboratory Assessments: Added that urinary protein/creatinine ratio is required in addition to standard laboratory assessments.

Section 8.2.1.4 Urinalysis: Added to state that at Main Screening, Cycle 1 Day 1, Cycle 1 Day 15, Day 1 of each subsequent cycle, and drug discontinuation, for proteinuria assessment follow instructions in Table 9. Also, reference to a proteinuria questionnaire removed as it was included in error.

Section 8.2.3 Vital signs: Clarification that the electronic devices provided measure pulse rate as well as blood pressure.

Version 6.0, 05 November 2019
Initial creation

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

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1 PROTOCOL SUMMARY

1.1 Schedule of Activities (SoA)

The Schedule of Activities (SoA) for the on-treatment period for Module 7 is shown in Table 1 below. For the SoA for the pre-screening and main-screening visits, please refer to the core protocol.

Table 1 Schedule of Activities – Treatment intervention period (Module 7)

	C1 28 days Weeks 1-4		C2 28 days Weeks 5-8		C3 28 days Weeks 9-12	C4 28 days Weeks 13-16	C5 - etc All cycles 28 days	Study drug disc. (28 days after study drug disc.)	Safety follow-up (90 days after study drug disc.)	Survival follow-up	Notes
Week (assuming no dose delays)	**1**	**3**	**5**	**7**	**9**	**13**	**17, 21, 25, 29, etc**				
Cycle day	**1**	**15**	**1**	**15**	**1**	**1**	**1**				
Window (days)	**0[a]**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±7**	**±7**	**±7**	
Study procedures[h]											
Physical examination	X	X	X	X	X	X	X	X			Section 8.2.2 (core protocol)
Vital signs[b]	X	X	X	X	X	X	X	X			Section 8.2.3 (core protocol). BP assessed twice-daily (Section 8.2.3 [this module])
ECG	X	As clinically indicated									Section 8.2.4 (core protocol)
ECHO/MUGA[c]	X					X	X				Section 8.2.5 (this module)
Concomitant medications	X	X	X	X	X	X	X	X			Section 6.5
Laboratory assessments[h]											
Clinical chemistry	X	X	X	X	X	X	X	X			Section 8.2.1 (core protocol). If screening laboratory assessments are performed within 3 days prior to Day 1 they do not need to be repeated at Day 1
Haematology	X	X	X	X	X	X	X	X			
APTT and INR	X	As clinically indicated[d]									
TSH, free T_3, and free T_4	X	X	X	X	X	X	X	X			Section 8.2.1 (core protocol)
Urinalysis[e]	X	X	X		X	X	X	X			Section 8.2.1 (core protocol) and Section 8.2.1.4 (this module)

Table 1 Schedule of Activities – Treatment intervention period (Module 7)

	C1 28 days Weeks 1-4		C2 28 days Weeks 5-8		C3 28 days Weeks 9-12	C4 28 days Weeks 13-16	C5 - etc All cycles 28 days	Study drug disc. (28 days after study drug disc.)	Safety follow-up (90 days after study drug disc.)	Survival follow-up	Notes
Week (assuming no dose delays)	**1**	**3**	**5**	**7**	**9**	**13**	**17, 21, 25, 29, etc**				
Cycle day	**1**	**15**	**1**	**15**	**1**	**1**	**1**				
Window (days)	**0[a]**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±7**	**±7**	**±7**	
Pregnancy test	X		X		X	X	X	X			Section 8.2.1.2 (core protocol)
AE/SAE assessment	X	X	X	X	X	X	X	X	X		Section 8.3 (core protocol)
Study drug administration[h]											
Durvalumab	X		X		X	X	X				See Section 6.2.1
Cediranib (5 days on, 2 days off)	X (5 days on, 2 days off every week)[f]										See Section 6.2.2 and 6.2.3
Drug accountability	X		X		X	X	X				Section 6.2.5
Other assessments											
Blood for ctDNA assessments	X	X	X	X	X	X	X (C5D1, C6D1, then every 3 cycles)	X			Section 8.8 (core protocol)
Circulating soluble factors (plasma)	X	X	X			X		X			Section 8.8 (core protocol)
Whole blood for gene expression (PaxGene RNA tubes)	X	X	X			X		X			Section 8.8 (core protocol)
PBMCs for flow cytometry (activation by / PD-1 CD8+)	X	X	X			X					Section 8.8 (core protocol)

Table 1 Schedule of Activities – Treatment intervention period (Module 7)

	C1 28 days Weeks 1-4		**C2** 28 days Weeks 5-8		**C3** 28 days Weeks 9-12	**C4** 28 days Weeks 13-16	**C5 - etc** All cycles 28 days	**Study drug disc.** (28 days after study drug disc.)	**Safety follow-up** (90 days after study drug disc.)	**Survival follow-up**	**Notes**
Week (assuming no dose delays)	**1**	**3**	**5**	**7**	**9**	**13**	**17, 21, 25, 29, etc**				
Cycle day	**1**	**15**	**1**	**15**	**1**	**1**	**1**				
Window (days)	**0[a]**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±7**	**±7**	**±7**	
TCR immune-sequencing	X	X	X			X					Section 8.8 (core protocol)
Blood sample for ADA for durvalumab (pre-dose except at safety follow up)	X		X				X (C5D1) then Q12W in first year, then Q24W in second year		X		Section 8.5.3 (core protocol)
Blood sample for PK of cediranib (pre-dose and 2 hours post-dose)			X			X					Section 8.5 (core protocol)
Tumour evaluation (CT or MRI) (RECIST 1.1)		Every 6 weeks ±1 week for the first 24 weeks relative to the date of first dose (Cycle 1 Day 1), then every 8 weeks ± 1 week thereafter, until objective disease progression as defined by RECIST 1.1 and confirmed with a subsequent scan (in the absence of clinically significant deterioration)									Section 8.1 (core protocol)
Biopsy on-treatment (mandatory)				X							Section 8.8 (core protocol). This should align with the first RECIST assessment.
Biopsy on disease progression								X			Section 8.8 (core protocol)

Table 1	**Schedule of Activities – Treatment intervention period (Module 7)**										
	C1 28 days Weeks 1-4		**C2** 28 days Weeks 5-8		**C3** 28 days Weeks 9-12	**C4** 28 days Weeks 13-16	**C5 - etc** All cycles 28 days	**Study drug disc.** (28 days after study drug disc.)	**Safety follow-up** (90 days after study drug disc.)	**Survival follow-up**	**Notes**
Week (assuming no dose delays)	**1**	**3**	**5**	**7**	**9**	**13**	**17, 21, 25, 29, etc**				
Cycle day	**1**	**15**	**1**	**15**	**1**	**1**	**1**				
Window (days)	**0[a]**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±7**	**±7**	**±7**	
Subsequent cancer therapy									X	X	Section 8.1.3.1 (core protocol). Every 3 months
Survival status										X[g]	Section 8.1.3.1 (core protocol). Every 3 months

[a] Every effort should be made to minimise the time between allocation to treatment and starting treatment. Note, if main screening assessments have been performed within 3 days prior to C1D1, then assessments do not need to be performed on C1D1 pre-dose.

[b] In addition to the standard vital signs assessments being conducted in HUDSON, in Module 7 patients must also have morning and evening blood pressure assessments (see Section 8.2.3)

[c] Patients who have any of the following should undergo an echocardiogram or MUGA (note: the same test must be used for the subject throughout the study) at baseline and every 4 cycles while on study (C4D1, C8D1 C12D1 etc), and if clinically indicated: A New York Heart Association classification of II controlled with treatment; Prior treatment with anthracyclines; Prior treatment with trastuzumab; Prior central thoracic radiation therapy, including radiotherapy to the heart; History of myocardial infarction within the prior 12 months or history of other significant impaired cardiac function (Section 8.2.5).

[d] For patients taking warfarin, it is recommended that INR and APTT be monitored carefully at least once per week for the first month, then monthly if the INR is stable.

[e] At Main Screening, Cycle 1 Day 1, Cycle 1 Day 15, Day 1 of each subsequent cycle, and drug discontinuation, for proteinuria assessment follow instructions in Table 9.

[f] Cediranib is administered orally on an intermittent schedule (5 days on, 2 days off) every week, starting on Cycle 1 Day 1 for durvalumab. Durvalumab is administered via IV infusion Q4W ±2 days. Durvalumab should be given at least 1 hour after the patient has taken their cediranib morning dose (on cediranib dosing days). For subsequent cycles, directly prior to the Day 1 for durvalumab infusion there should have been the 2 days off cediranib.

[g] Ad hoc collection of survival status may be requested for overall survival analyses.

[h] Following the final data cut-off for the module CSR (see Section 9.4.2 of the core protocol), any patients on study treatment may continue on treatment and should be assessed for safety according to standard local clinical practice. Study drug administration, SAE reporting and related safety assessment data should be recorded in the eCRF until 90 days after study drug discontinuation, when the patient will end participation in the study. The other assessments for the study will no longer be performed and those data will no longer be collected; the tumour evaluations will be performed as per standard of care. The survival follow-up will no longer be conducted.

ADA anti-drug antibodies; AE adverse event; APTT activated partial thromboplastin time; C cycle; CD8+ cytotoxic T-cell; CSR clinical study report; CT computed tomography; ctDNA, circulating tumour DNA; D day; ECG electrocardiogram; ECHO echocardiogram; eCRF electronic Case Report Form; INR international normalised ratio; RECIST Response Evaluation Criteria in Solid Tumours 1.1; MRI magnetic resonance imaging; MUGA, multigated acquisition scan; PBMC, peripheral blood mononuclear cell; PD-1 programmed cell death-1; Q12W every 12 weeks; Q24W every 24 weeks; Q4W every 4 weeks; SAE serious adverse event; TCR T-cell receptor repertoire; TSH thyroid-stimulating hormone; T_3 triiodothyronine; T_4 thyroxine.

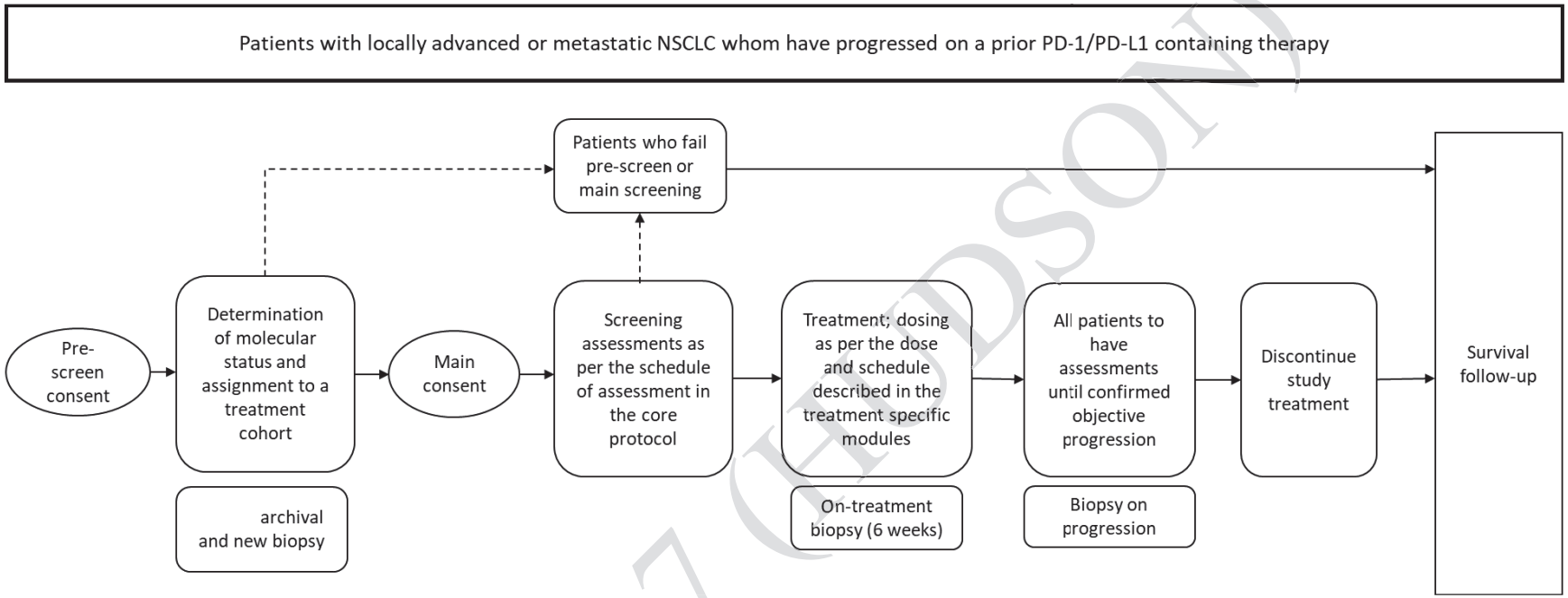
1.2 Synopsis

Please refer to Section 1.2 of the core protocol.

1.3 Schema

The general study design is summarised in Figure 1.

Figure 1 Study design



Note: From implementation of protocol v10.0, survival follow-up of screen failures is no longer applicable.

ctDNA circulating tumour DNA; NSCLC non-small cell lung cancer; PD-1 programmed cell death 1; PD-L1 programmed cell death ligand 1.

2 INTRODUCTION

Study D6185C00001 (HUDSON) is a Phase II, open-label, multi-centre umbrella study in patients who have received an anti-programmed cell death 1 (PD-1)/anti-programmed cell death-ligand 1 (PD-L1) containing therapy and a platinum doublet regimen for locally advanced or metastatic non-small cell lung cancer (NSCLC) either separately or in combination. The patient must have had disease progression on a prior line of anti-PD-1/PD-L1 therapy. The modular design allows the evaluation of the efficacy, safety, and tolerability of multiple study drugs. This module to the core study protocol describes Module 7, which will investigate the efficacy, safety, and tolerability of durvalumab administered in combination with cediranib (AZD2171).

2.1 Study rationale

As described in Section 2.2 of the core protocol, immune checkpoint inhibitors targeting the PD-1/PD-L1 pathway have shown significant activity in the first- and second-line treatment settings in patients with NSCLC. However, it is becoming evident that there is a new and significant patient population emerging that does not respond to anti-PD-1/PD-L1 containing therapy (primary resistance) or progresses during anti-PD-1/PD-L1 containing therapy (acquired resistance). There is currently no established therapy for patients who have received immune checkpoint inhibitors and platinum-doublet therapies, and novel treatments for these patients are urgently needed.

The aim of this umbrella study (D6185C00001) is to investigate multiple study drugs for the treatment of NSCLC in molecularly matched and non-matched patient populations after failure of immune checkpoint inhibitors, to identify patient populations who may respond favourably to novel anti-tumour therapies.

2.2 Background

Durvalumab and cediranib are both currently in clinical development as anti-cancer therapies in a variety of malignancies.

Durvalumab as a weight-based regimen of 10 mg/kg every 2 weeks (Q2W) has been approved for use in the treatment of patients with urothelial carcinoma (UC). On 16 February 2018, durvalumab was approved in the US for the treatment of patients with unresectable Stage III NSCLC. On 21 September 2018, durvalumab was approved in the European Union (EU) for the treatment of locally advanced, unresectable NSCLC in adults whose tumours express PD-L1 on ≥1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy. As of 12 July 2019, durvalumab is approved in over 45 countries for NSCLC. On 27 March 2020, the Food and Drug Administration approved durvalumab in combination with etoposide and either carboplatin or cisplatin as first-line treatment of patients with extensive-stage small cell lung cancer.

Module 7 will investigate both agents in combination, to test the hypothesis that the combination will result in complementary anti-tumour activity. Brief background on durvalumab and cediranib, including their mechanisms of action, is provided below. For detailed descriptions of the chemistry, pharmacology, efficacy, and safety of durvalumab and cediranib, please refer to the respective Investigator's Brochures.

The study will recruit biomarker non-matched patients (see Section 4.1).

2.2.1 Durvalumab

2.2.1.1 Overview of durvalumab

Expression of PD-L1 protein is an adaptive immune response that helps tumours evade detection and elimination by the immune system. PD-L1 can be induced by inflammatory signals (eg, interferon-gamma) and can be expressed on both tumour cells and tumour-associated immune cells in tumour microenvironment. PD-L1 blocks T-cell function and activation through interaction with PD-1 and CD80 (B7.1). By binding to its receptors, PD-L1 reduces cytotoxic T-cell activity, proliferation, and cytokine production. Durvalumab is a fully human, high affinity, immunoglobulin G1 kappa monoclonal antibody that selectively blocks the interaction of PD-L1 with PD-1 and cluster of differentiation (CD)80 (B7.1) while leaving PD-1/ programmed cell death ligand-2 interaction intact. Durvalumab does not induce antibody dependent cell-mediated cytotoxicity. Selective blockade of PD-L1/PD-1 and PD-L1/CD80 interactions enhances antitumour immune responses. These antitumour responses may result in tumour elimination.

Durvalumab is approved in a number of territories including the US, EU, Japan, Canada and Brazil under the brand name IMFINZI Injection.

The recommended dose as per the IMFINZI package insert is 10 mg/kg administered as an IV infusion over 60 minutes every 2 weeks (Q2W).

For more information, please refer to the latest version of the durvalumab Investigator's Brochure.

2.2.1.2 Durvalumab data

To date, durvalumab has been given to more than 12000 patients as part of ongoing studies either as monotherapy or in combination with other anticancer agents. Details on the safety profile of durvalumab monotherapy are summarised below. Refer to the current durvalumab IB for a complete summary of pre-clinical and clinical information including safety, efficacy, and pharmacokinetics (PK).

Clinical activity in locally advanced NSCLC

The efficacy of durvalumab was evaluated in the PACIFIC Study, a randomised, double-blind, placebo-controlled, multicentre study in 713 patients with histologically or cytologically confirmed locally advanced, unresectable NSCLC. Patients had completed definitive platinum-based chemoradiation within 1 to 42 days prior to initiation of the study and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Ninety-three percent of patients had received a total dose of 54 to 66 Gy of radiation. The study excluded patients who had progressed following concurrent chemoradiation therapy, patients with active or prior documented autoimmune disease within 2 years of initiation of the study; a history of immunodeficiency; a history of severe immune-mediated adverse reactions; medical conditions that required systemic immunosuppression, except physiological dose of systemic corticosteroids; active tuberculosis or hepatitis B or C or HIV infection or patients receiving live attenuated vaccine within 30 days before or after the start of durvalumab. Patients were randomised 2:1 to receive 10 mg/kg durvalumab (n=476) or 10 mg/kg placebo (n=237) via IV infusion Q2W for up to 12 months or until unacceptable toxicity or confirmed disease progression. Randomisation was stratified by gender, age (<65 years vs. ≥65 years) and smoking status (smoker vs. nonsmoker). Patients with disease control at 12 months were given the option to be re-treated upon disease progression. Tumour assessments were conducted every 8 weeks for the first 12 months and then every 12 weeks thereafter.

The demographics and baseline disease characteristics were well balanced between study arms. Baseline demographics of the overall study population were as follows: male (70%), age ≥65 years (45%), White (69%), Asian (27%), other (4%), current smoker (16%), past-smoker (75%), and never smoker (9%), World Health Organisation (WHO)/ECOG PS 0 (49%), WHO/ECOG PS 1 (50%). Disease characteristics were as follows: Stage IIIA (54%), Stage IIIB (44%), histological subgroups of squamous (47%), non-squamous (53%), PD-L1 expression in tumour cells (TC)≥25% (22%), PD-L1 expression TC<25% (41%). (PD-L1 status was retrospectively analysed using the Ventana PD-L1 [SP263] Assay in 451 patients with available samples, taken prior to concurrent chemoradiation therapy).

At the time of the interim progression-free survival (PFS) analysis, the median PFS by blinded independent central review (BICR) was significantly longer with durvalumab treatment (16.8 months) compared with placebo (5.6 months); hazard ratio 0.52; 98.9% CI: 0.39, 0.70; p<0.0001. At the time of the interim overall survival (OS) analysis, the median OS was not reached for the durvalumab arm and was 29.1 months for the placebo arm; hazard ratio, 0.69; 95% CI, 0.55, 0.86). The 36-month OS rate was 57.0% with durvalumab vs 43.5% with placebo.

Clinical activity in recurrent and metastatic NSCLC

Based on current data from the ongoing Study CD-ON-MEDI4736-1108 (NCT01693562), evidence of clinical activity with durvalumab has been observed. The following responses were observed in patients with NSCLC.

Overall, clinical activity was observed in both the PD-L1 high (defined as having tumour cells [TC] ≥25%) and PD-L1 low/negative (defined as TC <25%) subgroups, however, patients with PD-L1 high tumours had higher objective response rates (ORRs).

The ORR per BICR was 21.8% and 6.4% in patients with PD-L1 high and low/negative tumours, respectively and 15.3% in the overall population regardless of PD-L1 expression. The ORR was 25.9%, 14.3% and, 11.5% in the 1L, 2L and 3L+ cohorts, respectively. Median duration of response (DOR) was 17.74 months. Median OS was 12.4 months; median OS was 21.0, 11.8 and 9.3 months in the 1L, 2L and 3L+ cohorts, respectively. The OS rate at 24 months was 29.6%.

The ATLANTIC study in third-line or higher NSCLC showed higher ORR and survival outcomes in high PD-L1 positive patients. Across cohorts the ORR ranged from 3 to 43%, median PFS ranged from 1.8 to 5.5 months and median OS ranged from 5.9 to 13.6 months but was not reached at the time of initial reporting in the >90% PD-L1 expressors. The ORR and survival outcomes reported in durvalumab studies are in keeping with other similar agents targeting the PD-1/PD-L1 axis (Garassino et al 2017).

Preliminary efficacy data from the MYSTIC study in first-line advanced or metastatic NSCLC showed that in PD-L1 high (≥25% TC) NSCLC, median PFS by BICR was 4.7 months for durvalumab monotherapy and 5.4 months for chemotherapy; hazard ratio of 0.87; 99.5% CI: 0.593, 1.285; p=0.324. The median OS was 16.3 months for the durvalumab arm and 12.9 months for the chemotherapy arm; hazard ratio for death was 0.76; 97.54% CI: 0.564, 1.019; p=0.036. The 24-month OS rate was 38.3% vs 22.7% and the 12-month PFS rate was 32.3% vs 14.3% for the durvalumab and chemotherapy arms respectively. When durvalumab was administered in combination with tremelimumab, the median PFS by BICR was 3.9 months for durvalumab + tremelimumab and 5.4 months for chemotherapy; hazard ratio of 1.05; 99.5% CI: 0.722, 1.534; p=0.705. The median OS was 11.9 months for the durvalumab + tremelimumab arm and 12.9 months for the chemotherapy arm; hazard ratio for death was 0.85; 98.77% CI: 0.611, 1.173; p=0.202. The 24-month OS rate was 35.4% vs 22.7% and the 12-month PFS rate was 25.8% vs 14.3% for the durvalumab + tremelimumab and chemotherapy arms respectively.

Immuno-oncology agents targeting the PD-1/PD-L1 pathway have demonstrated activity as monotherapy and in combination with chemotherapy in patients who are immunotherapy-naïve. However, the present study will recruit patients who either have primary resistance to anti-PD-1/PD-L1 therapy or who developed acquired resistance while on anti-PD-1/PD-L1 therapy. Thus, in this immunotherapy-resistant setting, durvalumab will be administered in combination with an agent that has a different and complementary mechanism of action in order to maximise the likelihood of clinical activity.

2.2.2 Cediranib

2.2.2.1 Overview of cediranib

Cediranib (AZD2171) is a potent small molecule vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitor of all three VEGF receptors (VEGFR-1, -2 and -3) at nanomolar concentrations. Inhibition of VEGF signalling leads to the inhibition of angiogenesis, lymphangiogenesis, neovascular survival and vascular permeability. Cediranib has additional activity against stem cell factor receptor (c-kit) tyrosine kinase inhibiting this kinase with a similar potency to that at which it inhibits VEGFRs. Cediranib is less active versus platelet-derived growth factor receptor (PDGFR) tyrosine kinases, and inactive against other kinases tested.

Cediranib inhibited the growth of tumours in preclinical models in a dose-dependent manner. At doses that reduce tumour growth VEGFR-2 and c-kit were inhibited, but only partial inhibition of PDGFR was observed. Anti-tumour activity was associated with a reduction in micro-vessel density and changes in vascular permeability. Cediranib reduced ascites accumulation in pre-clinical models of ovarian cancer. Cediranib also inhibited metastatic dissemination in pre-clinical models, and through inhibition of VEGFR-3 inhibited lymphangiogenesis. Collectively, these changes indicate that cediranib limits tumour growth, metastases and microvascular permeability. Following once daily (od) dosing with 20 mg cediranib, the unbound minimum steady-state plasma concentration ($C_{ss,min}$) was approximately 5-fold greater than the human umbilical vein endothelial cell proliferation inhibitory concentration 50% (IC_{50}) reported in non-clinical studies. At a clinical dose of 20 mg in patients, a small increase in diastolic blood pressure (DBP) and systolic blood pressure (SBP) is expected; a significant reduction in serum soluble VEGFR2 has been observed; and a decrease in tumour vessel permeability and vascularity in liver lesions, as measured by dynamic contrast enhanced magnetic resonance imaging, has been detected.

2.2.2.2 Cediranib data

As of 20 July 2019, the overall safety profile of cediranib is based on data from approximately 2980 patients treated in AstraZeneca sponsored trials. These patients had various malignancies and were exposed to cediranib in combination with chemotherapy or as monotherapy, at doses ranging from 0.5 to 90 mg (including 33 patients who have received cediranib in a Named Patient Supply programme). Additionally, approximately 5524 patients have been enrolled in clinical trials in investigator led or collaborative group sponsored studies in which cediranib was supplied in one or more treatment arms.

Cediranib has been evaluated in a broad clinical programme that includes both monotherapy and combination studies, in multiple tumour types, including ovarian cancer, colorectal cancer, glioblastoma, NSCLC, renal cell carcinoma, alveolar soft part sarcoma, as well as a large number of signal-searching studies in a range of other tumour types. There are no clinical studies with

cediranib involving healthy volunteers. An overview of the most relevant efficacy and safety findings is provided below; for further details see the Investigator's Brochure.

Efficacy

Platinum-sensitive relapsed ovarian cancer:

Improvements in median PFS have been observed for combinations of concurrent chemotherapy/cediranib (174 patients) and concurrent chemotherapy/cediranib + cediranib maintenance (164 patients) compared with chemotherapy/placebo (118 patients) (ICON6 study: median PFS for cediranib concurrent/maintenance was 11.0 months compared with 8.7 months for chemotherapy/placebo (HR 0.57 [95% CI: 0.44, 0.73; p<0.001]). The ORR was higher for cediranib concurrent/maintenance [65.1%] and concurrent chemotherapy/cediranib arms (63.2%) compared with the chemotherapy/placebo arm [53.4%]).

Improvements in median PFS have also been observed for cediranib/olaparib (44 patients) compared with olaparib alone (46 patients) (NCI-8348 study: median PFS was 17.7 months for the cediranib/olaparib arm compared with 9.0 months for the olaparib alone arm [HR 0.42; 95% CI: 0.23, 0.76; p=0.005]. The ORR was 79.6% for the cediranib/olaparib arm compared with 47.8% for the olaparib alone arm [odds ratio 4.24; 95% CI: 1.53, 12.22; p=0.002]).

Non-small cell lung cancer

Efficacy data for the NSCLC programme include data from 1 exploratory, open-label, multicentre study (Study 15) and 1 Phase I/II multi-centre 2-part study in Japanese patients, which was terminated prematurely (Study 40). Data are also available for NCI-sponsored studies (BR24 and BR29).

In Study 15, the mean best percentage change was a 25.9% reduction in tumour size and consistent changes in FDG-PET were observed. In Study 40, 2 patients in the cediranib 30 mg + paclitaxel/carboplatin group had partial responses and 2 patients in the cediranib 20 mg + paclitaxel/carboplatin group had a best response of SD.

In Study BR24, the addition of cediranib to carboplatin/paclitaxel resulted in improved response and numerical improvement in PFS, but did not appear tolerable at a 30 mg dose (Goss et al 2010).

Study BR29, which studied cediranib 20 mg, was halted for futility at the interim analysis (HR for PFS 0.89; 95% CI 0.66, 1.20; p=0.45) (Laurie et al 2014). A final analysis was performed on all 306 enrolled patients. The addition of cediranib to carboplatin/paclitaxel increased response rate (52% versus 34%; p=0.001) but did not significantly improve PFS (HR 0.91; 95% CI 0.71, 1.18; p=0.49) or OS (HR 0.94; 95% CI 0.69, 1.30; p=0.72).

Other tumour types

For efficacy data on other tumour types, see the Investigator's Brochure.

Safety

A summary of the key safety findings for cediranib from clinical studies is presented below. For further details of the individual studies, see the Investigator's Brochure.

- Diarrhoea, severe fatigue, arterial thromboembolism and posterior reversible encephalopathy syndrome (PRES) are considered important identified risks for cediranib. Hypertension, fistulae and GI perforation are class effects of VEGF signalling inhibitors that are already reasonably characterised and have been reported in the cediranib development programme with a similar frequency and severity as observed with the other VEGF signalling inhibitors or are manageable within current practice. Severe neutropenia, including febrile neutropenia, is not considered an important identified risk for cediranib in combination with platinum/paclitaxel chemotherapy because in oncology, severe neutropenia is manageable as per local practice in association with cediranib/chemotherapy dose modifications.
  - A low incidence of important known class effects such as GI perforation, fistulae, arterial thromboembolism and PRES was reported in patients treated with cediranib; these events were generally reversible, but some patients recovered with sequelae.
- Venous thromboembolic events, including pulmonary embolism and deep vein thrombosis, have been reported in patients treated with cediranib.
- Bleeding/haemorrhagic events have been reported in patients treated with cediranib, with mild to moderate epistaxis being the most frequently reported event.
- Proteinuria, thyroid dysfunction and wound healing impairment have been reported in patients treated with cediranib.
- Based on data from cediranib studies and known class effects of other VEGF inhibitors, symptomatic left ventricular dysfunction/cardiac failure, nephrotic syndrome, renal thrombomicroangiopathy, liver failure and effects on embryofoetal development and survival are considered important potential risks for cediranib.
- Cumulative review of the global safety database across the cediranib programme identified 2 patients with SAEs of hepatic failure and a single patient with an SAE of drug-induced liver injury (DILI). None of the reports of abnormalities in liver function parameters were consistent with the criteria of Hy's Law. A causal relationship has not been established between cediranib treatment and the AE of liver failure.
- No clinically relevant differences in ALT, AST, and bilirubin concentrations were observed between the cediranib concurrent/maintenance group and the chemotherapy + placebo group in the combination therapy pool throughout the chemotherapy and maintenance phases.
- Patients with mild and moderate renal impairment discontinued cediranib more often due to adverse events, particularly when cediranib was co-administered with chemotherapy.
- No data are available in patients with severe (creatinine clearance <30 mL/min) renal impairment or patients on dialysis.
- Cediranib is not associated with the potential for QTc interval prolongation.

- Mild reversible changes in LVEF were observed in patients treated with cediranib, which were not considered clinically significant as they did not result in clinical symptoms or require additional standard monitoring.

The safety profile of cediranib is fairly consistent across indications and in keeping with the known profile of VEGFR inhibitors. Knowledge of the cediranib safety profile and early management of toxicities reduces the incidence of discontinuations due to adverse events. Patients should have a central role in recognising early signs of diarrhoea and initiating anti-diarrhoeal treatment as instructed, as well as monitoring BP from treatment initiation and throughout the course of cediranib treatment.

2.2.3 Durvalumab and cediranib in combination

Cediranib has been investigated in NSCLC in combination with chemotherapy. A Phase I study (BR24) looking at the addition of daily cediranib to carboplatin and paclitaxel showed improved response rates and PFS (Section 2.2.2.2) but did not appear tolerable at the 30 mg dose daily orally administered cediranib (Goss et al 2010). Cediranib patients were more likely to experience all causality severe hypertension, GI toxicity (diarrhoea, anorexia, mucositis), febrile neutropenia, fatigue, granulocytopenia, and thrombocytopenia as well as more all-grade, all-causality dyspnoea and hand-foot syndrome compared with patients on placebo. In a subsequent study (BR29), cediranib was dose reduced to 20 mg daily and showed an improvement in response rate but did not improve PFS or OS (Section 2.2.2.2; Laurie et al 2014). However, there is emerging data about the potential for multi-targeted anti-angiogenic tyrosine kinase inhibitors further potentiate the anti-tumour immune response (Galluzzi et al 2012). VEGF suppresses lymphocyte trafficking across endothelial cells and sites of inflammation to promote vessel growth (Kandalaft et al 2011;Motz et al 2014). VEGF reduces the anti-tumour immune response, including inhibiting the T cell responses and increasing regulatory T cell proliferation (Oelkrug and Ramage 2014).

A Phase I study has been completed in women's cancers assessing the combination of durvalumab and cediranib (Lee et al 2016). A total of 14 patients were dosed with this combination (8 patients received cediranib 20 mg once daily; 6 patients received cediranib 20 mg 5 days on 2 days off), and the study established a recommended Phase II dose of the combination in addition to demonstrating preliminary evidence of durable activity. The combination in this population (primarily ovarian cancer) showed increased activity (50% ORR) compared to cediranib alone (17%) or anti-PD-1/PD-L1 therapy (11% to 17%) alone based on historical controls (Lee et al 2017; Hamanishi et al 2015; Bourla and Zamarin 2016; Petit and Basu 2013; Matulonis et al 2019). Four patients who received cediranib once daily had PK samples collected on Day 1 (before durvalumab co-administration) and Day 15 (after durvalumab co-administration); in 2 of the 4 patients, cediranib exposure increased ~3-fold following co-dosing with durvalumab; it is not clear if the increase in cediranib exposure in these 2 patients was due to durvalumab co-administration or other reasons (Lee et al 2017). A daily cediranib dose of 20

mg was not well tolerated in this study (Grade 4 events of lymphopenia and pulmonary thromboembolism, and Grade 3 events of lymphopenia, anaemia, nausea, diarrhoea, colitis, fatigue headache, hypertension, pulmonary thromboembolism and pulmonary hypertension); however tolerability was much improved in the 6 patients who received a dose of 20 mg 5 days on 2 days off (1 Grade 4 event of hypertension, and 1 Grade 3 event of fatigue) (see also Section 4.3.2).

This module in Study D6185C00001 (Module 7) is for a combination therapy of durvalumab plus cediranib. Module 7 will investigate the safety, tolerability, and anti-tumour activity of cediranib in combination with durvalumab in Cohort B.7.ACQ.

2.3 Benefit/risk assessment

As described in Section 2.3 of the core protocol, patients recruited to this study are not expected to have other treatment options apart from monotherapy chemotherapy, such as docetaxel. The survival outcome and toxicity profile of chemotherapy in this setting mean that other active therapies are highly desirable and present a potential advantage for patients.

Overall, preliminary findings support a favourable benefit risk profile for cediranib in combination with durvalumab. Evaluation of the safety profiles of durvalumab and cediranib revealed that there is limited potential for potentiation of the known adverse drug reactions of both agents, due to the different pharmacological mechanisms of action. Management of shared toxicities of cediranib and durvalumab is described in Section 8.4.5.3. Additionally, several measures, including project-specific safety related inclusion/exclusion criteria, physical examinations, evaluation of AEs/serious adverse events (SAEs) and laboratory testing throughout the study and study treatment modifications and toxicity management guidelines have been incorporated into this study protocol to mitigate any potential or identified risks associated with these agents.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of cediranib and durvalumab can be found in the respective Investigator's Brochures.

3 OBJECTIVES AND ENDPOINTS

Please refer to the core protocol.

4 STUDY DESIGN

4.1 Overall design

This is an open-label, multi-centre, umbrella study in patients who have received an anti-PD-1/PD-L1 containing therapy and a platinum doublet regimen for locally advanced or metastatic NSCLC either separately or in combination. The patient must have had disease

progression on a prior line of anti-PD-1/PD-L1 therapy. For details on the study treatments given in Module 7, see Section 6.1 of this module.

Module 7 will evaluate the efficacy, safety, and tolerability of durvalumab (given intravenously [IV]) in combination with cediranib (given orally) in 1 cohort of patients as follows:

- **Cohort B.7.ACQ** will investigate the efficacy, safety, and tolerability of durvalumab given IV, in combination with cediranib given orally in patients with acquired resistance (Cohort B.7.ACQ).

A study flow diagram is provided in the core protocol (Figure 4).

4.2 Scientific rationale for study design

The study aims to identify patient populations who may respond favourably to novel anti-tumour therapies, and the modular design allows evaluation of the efficacy, safety, and tolerability of multiple study drugs. Owing to the different schedules and routes of administration of the study drugs, the study requires an open-label design.

VEGF ligands (VEGF-A, B, C and PlGF) contribute to creating an immunosuppressive microenvironment through regulation of different cells types (endothelium, Tregs, myeloid cells) through VEGFR1, 2 and 3. Reversing the immunosuppressive VEGF-mediated signalling will enhance the ability of durvalumab to sustain T cell activation in lung tumours. This could suggest that inhibition of VEGF-signalling can reverse resistance to immunotherapy in this patient population, and cediranib is an inhibitor of the VEGF receptor tyrosine kinase. Other VEGF signalling inhibitors have shown improved clinical benefit when combined with PD-1 or PD-L1 inhibitors in renal cancer and lung cancer and other tumour types, eg, the combination of bevacizumab, PD-1 and chemotherapy has given improved responses in lung cancer (IMpower150 Socinski et al 2018). In IMpower150, the addition of atezolizumab to bevacizumab plus chemotherapy significantly improved PFS and OS among patients with metastatic non-squamous NSCLC, regardless of PD-L1 expression. The PFS was longer in the atezolizumab/bevacizumab/chemotherapy arm compared with bevacizumab/chemotherapy [median PFS 8.3 versus 6.8 months; HR 0.62; 95% CI: 0.52, 0.74; p<0.001]. Survival was longer in the atezolizumab/bevacizumab/ chemotherapy arm compared with bevacizumab/chemotherapy (median OS 19.2 versus 14.7 months; HR 0.78; 95% CI 0.64, 0.96; p=0.02; 12-month OS 67% versus 61%). Results from IMpower150 place the combination of atezolizumab and bevacizumab with carboplatin and paclitaxel as a therapeutic option in patients with PS 0–1 with metastatic non-squamous NSCLC, in absence of contraindications to use of immunotherapy. This combination does, however, carry a significant toxicity burden, with CTCAE Grade 3 or 4 events being primarily haematological in nature (see cediranib Investigator's Brochure for further details on cediranib safety).

There are several other clinical trials investigating the anti-VEGF pathway in combination with PD-1 or PD-L1 inhibitors in NSCLC including a combination of axitinib and avelumab (NCT03472560), the combination with lenvatinib and pembrolizumab in NSCLC (NCT03829332), and a Phase 3 Study of sitravatinib and nivolumab vs docetaxel in patients with advanced NSCLC (NCT03906071).

4.3 Justification for dose

4.3.1 Justification for durvalumab dose

A durvalumab dose of 20 mg/kg Q4W is supported by in vitro data, pre-clinical activity, clinical PK/pharmacodynamics, biomarkers, and activity data from Study CD-ON-MEDI4736-1108 (hereafter referred to as Study 1108) in patients with advanced solid tumors and from a Phase I study performed in Japanese patients with advanced solid tumor (D4190C00002).

PK/Pharmacodynamic data

Based on available PK/pharmacodynamic data from ongoing Study 1108 with doses ranging from 0.1 to 10 mg/kg Q4W or 15 mg/kg Q4W, durvalumab exhibited non-linear (dose dependent) PK consistent with target-mediated drug disposition. The PK approached linearity at ≥3 mg/kg Q4W, suggesting near complete target saturation (membrane-bound and sPD-L1), and further shows that the durvalumab dosing frequency can be adapted to a particular regimen given the linearity seen at doses higher than 3 mg/kg. The expected half-life with doses ≥3 mg/kg Q4W is approximately 21 days. A dose-dependent suppression in peripheral sPD-L1 was observed over the dose range studied, consistent with engagement of durvalumab with PD-L1. A low level of immunogenicity has been observed. No patients have experienced immune-complex disease following exposure to durvalumab. (For further information on immunogenicity, please see the current durvalumab IB).

A population PK model was developed using the data from Study 1108 (doses=0.1 to 10 mg/kg Q2W or 15 mg/kg Q4W; Fairman et al 2014). Multiple simulations indicate that a similar overall exposure is expected following both 10 mg/kg Q4W and 20 mg/kg Q4W regimens, as represented by AUC_{ss} (4 weeks). Median $C_{max,ss}$ is expected to be higher with 20 mg/kg Q4W (~1.5 fold) and median $C_{trough,ss}$ is expected to be higher with 10 mg/kg Q4W (~1.25 fold). Clinical activity with the 20 mg/kg Q4W dosing regimen is anticipated to be consistent with 10 mg/kg Q4W with the proposed similar dose of 20 mg/kg Q4W expected to (a) achieve complete target saturation in majority of patients; (b) account for anticipated variability in PK, pharmacodynamics, and clinical activity in diverse cancer populations; (c) maintain sufficient PK exposure in case of ADA impact; and (d) achieve PK exposure that yielded maximal antitumor activity in animal models.

Given the similar area under the serum drug concentration-time curve (AUC) and modest differences in median peak and trough levels at steady state, the observation that both regimens

maintain complete sPD-L1 suppression at trough, and the available clinical data, the 20 mg/kg Q4W and 10 mg/kg Q4W regimens are expected to have similar efficacy and safety profiles, supporting further development with a dose of 20 mg/kg Q4W.

Clinical data

Refer to the current durvalumab IB for a complete summary of clinical information including safety, efficacy, and PK at the 20 mg/kg Q4W regimen.

Rationale for fixed dosing

A population PK model was developed for durvalumab using monotherapy data Study 1108 (N=292; doses = 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W; solid tumors). Population PK analysis indicated only minor impact of body weight on the PK of durvalumab (coefficient of ≤0.5). The impact of body weight-based (10 mg/kg Q2W) and fixed dosing (750 mg Q2W) of durvalumab was evaluated by comparing predicted steady state PK concentrations (5th, median, and 95th percentiles) using the population PK model. A fixed dose of 750 mg was selected to approximate 10 mg/kg (based on median body weight of ~75 kg). A total of 1000 patients were simulated using body weight distribution of 40 to 120 kg. Simulation results demonstrate that body weight-based and fixed dosing regimens yield similar median steady state PK concentrations with slightly less overall between-patient variability with fixed dosing regimen.

Similar findings have been reported by others (Narwal et al 2013, Ng et al 2006, Wang et al 2009, Zhang et al 2012). Wang and colleagues investigated 12 monoclonal antibodies and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies (Wang et al 2009). In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-patient variability in PK/pharmacodynamic parameters (Zhang et al 2012).

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar PK exposure and variability, AstraZeneca considered it feasible to switch to fixed dosing regimens. Based on average body weight of 75 kg, a fixed dose of 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) is included in the current study.

An exception to 1500 mg fixed dosing is made for patients with low body weight (below 30 kg). Patients with a body weight of 30 kg or less must receive weight-based dosing, equivalent to 20 mg/kg, until weight increases to greater than 30 kg. At this time, fixed dosing data for patients weighing below 30 kg (corresponding to doses greater than 50 mg/kg) are not available and are not yet supported by product development.

Thus, the clinical activity observed coupled with the safety profile, translational science correlates, and non-clinical data supports further development with a dose of 1500 mg Q4W. The dose of durvalumab will not be modified during the study.

4.3.2 Justification for cediranib dose

The pharmacokinetics of cediranib have been studied following single and repeat administration of a solution and tablet formulation in cancer patients. Once daily and intermittent dosing (5 consecutive days on, 2 days off) have been investigated, particularly in combination with durvalumab. The daily continuous dosing of 20 mg cediranib with durvalumab 1500 mg Q4W was declared not tolerated but 20 mg of cediranib daily for 5 days on/2 days off is tolerated) (Section 2.2.3; Lee et al 2017). In summary, cediranib is orally available, rapidly absorbed when administered as a tablet and has a terminal half-life of 22 hours when administered as a single agent. Single agent cediranib exposure increased proportionally with dose. Administration of cediranib once daily results in limited accumulation (typically 1-to 3-fold) with steady-state exposures achieved within 5 days.

Absorption of cediranib is not delayed following administration with food relative to the fasted state at doses of 20 mg or above although at doses of 15 mg it is recommended to dose on an empty stomach at least 1 hour before and 2 hours after a meal to ensure adequate exposure.

Cediranib is not metabolized by cytochrome P450 isoenzymes but alterations in exposure have been seen with potent inducers of UGT/Pgp. In addition, in vitro data suggest that cediranib is unlikely to cause interactions with CYP450 substrates. Cediranib is a substrate of MDR1 (Pgp), and a possible substrate of breast cancer resistant protein (BCRP). Cediranib has low potential to inhibit MDR1, BCRP, OATP1B1, OATP1B3, OCT2, and MATE1. The clinical impact of this finding is unknown. There are specific exclusion criteria and co-medication guidance in place to avoid potential PK drug interactions (see Sections 5.2 and 6.5 of this document).

Considering emerging PK data from ongoing studies, there is no evidence to indicate any dose adjustment based on race or ethnicity.

Assessment of cediranib and durvalumab safety profiles prior to the start of this study revealed that there is limited potential for potentiation of the known adverse drug reactions of both agents, due to the different pharmacological mechanisms of action. The 2 agents have some ADRs in common, eg, diarrhoea, rash (including rash of infusion-related reactions), hyper/hypothyroidism, fatigue and hepatic toxicity (Section 8.4.5.3), and there is a potential for an increased risk of these overlapping toxicities.

In the dose finding study (see also Section 2.2.3), patients received cediranib orally at 3 different dose levels starting at 20 mg daily with durvalumab at 10 mg/kg Q2W and then 30 mg daily of cediranib with durvalumab at 10 mg/kg Q2W. Although no patients met DLT criteria at these doses 7 out of 8 patients receiving the daily cediranib dosing discontinued due to recurrent

Grade 2 or non-DLT Grade 3 or 4 AEs (including grade 4 pulmonary thromboembolism adding to pulmonary hypertension and grade 3 colitis). PK analysis of these patients revealed an increased exposure to cediranib when administered daily in combination with durvalumab. A protocol amendment added a new dose level of cediranib 20 mg 5 days on, 2 days off in combination with durvalumab 1500 mg Q4W. This demonstrated improved tolerability with 2 out of 6 patients experiencing Grade 3 or Grade 4 toxicities; 1 patient had Grade 3 fatigue and one patient had Grade 4 hypertension (declared a DLT requiring dose reduction) with PK on the intermittent schedule showing the same exposure as with single agent cediranib at 20 mg dosing. The cediranib plus durvalumab combination has been evaluated in a total of 14 patients.

Within the limits of a small patient population, the combination of cediranib and durvalumab is well tolerated in the majority of cases, and no new safety signals have been observed.

Details of all cediranib studies, including externally sponsored research studies, are summarised in the Investigator's Brochure.

4.4 End of study definition

Please refer to core protocol.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study in order to assigned/randomised to a study cohort. Under no circumstances can there be exceptions to this rule. Patients who do not meet the entry requirements are screen failures; refer to Section 5.4 of the core protocol.

5.1 Module 7-specific inclusion criteria

Patients are eligible to be included in the study only if all the following inclusion criteria apply. Please refer to Section 5.1 of the core protocol for the inclusion criteria applicable to all modules in the study. Additional inclusion criteria applicable to Module 7 only are described below:

O-1. Patients must fulfil all the core eligibility criteria.

O-2. Adequately controlled blood pressure (SBP ≤140 mm Hg and DBP ≤90 mmHg) in the presence or absence of a stable regimen of antihypertensive therapy.

O-3 Patients must be able to swallow and retain oral medications and be without clinically significant gastrointestinal illnesses that would preclude absorption of cediranib.

O-4 Time to radiological progression on prior immunotherapy >24 weeks.

5.2 Module 7-specific exclusion criteria

Patients must not enter Module 7 if any of the following exclusion criteria apply. Refer to Section 5.2 of the core protocol for the exclusion criteria applicable to all modules in the study. Additional exclusion criteria applicable to Module 7 only are described below:

O-1 Inadequate renal function:

- Creatinine clearance (see core exclusion 18f) and
- Urine protein:creatinine ratio (UPC) >1 or >2+ proteinuria on 2 consecutive dipsticks taken no less than 1 week apart

Subjects with 2+ proteinuria on dipstick must also have UPC ≥0.5 on 2 consecutive samples.

O-2 History of gastrointestinal perforation. Patients with a history of abdominal fistula may be considered if fistula was surgically repaired and there is no evidence of fistula recurrence in the 6 months prior to study enrolment, and patient is considered low risk for recurrence of fistula in the opinion of the investigator.

O-3 Intra-abdominal abscess within 3 months prior to enrolment.

O-4 Clinically significant signs and/or symptoms of bowel obstruction within 3 months before study enrolment.

O-5 Patients with any 1 or more of the following:

- Myocardial infarction (MI) within the last 6 months prior to enrolment. Patients with a history of MI within 6 to 12 months prior to enrolment may be allowed following assessment and approval by the medical monitor/sponsor
- Known significant cardiac disease (see also core exclusion 17).

O-6 Left ventricular ejection fraction < lower limit of normal (LLN) per institutional guidelines, or <55%, if threshold for normal is not otherwise specified by institutional guidelines, for patients with the following risk factors:

- Prior or planned treatment with anthracyclines (ie, PLD)
- Prior treatment with trastuzumab
- Prior central thoracic radiation therapy (RT), including exposure of heart to therapeutic doses of ionizing RT
- History of myocardial infarction within 6 to 12 months prior to enrolment
- Prior history of other significant impaired cardiac function.

For procedures for withdrawal of incorrectly enrolled patients see Section 7.3 of the core protocol.

5.3 Lifestyle restrictions

5.3.1 Restrictions applicable to durvalumab

Patients should not donate blood or blood components while participating in this study and through 90 days after receipt of the final dose of durvalumab or until alternate anticancer therapy is started.

Immunosuppressive medications including, but not limited to systemic corticosteroids at doses beyond 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumour necrosis factor alpha blockers are prohibited. Use of immunosuppressive medications for the management of study drug-related AEs and in patients with contrast allergies is acceptable. In addition, use of inhaled and intranasal corticosteroids is permitted (see Table 3).

Live attenuated vaccines within 30 days of durvalumab dosing are prohibited (ie, 30 days prior to the first dose, during treatment with durvalumab and for 180 days post discontinuation of durvalumab) (see Table 3). Inactivated viruses, such as those in the influenza vaccine or authorised and approved Coronavirus Disease 2019 (COVID-19), are permitted (see Table 4).

5.3.2 Restrictions applicable to cediranib

Please refer to Section 5.3 of the core protocol for contraception requirements.

5.3.2.1 Meals and dietary restrictions

At the 20 mg daily dose level, adequate free systemic exposure for inhibition of VEGFR2 is maintained even after food reduces the exposure; therefore, cediranib can be administered with or without food at the 20 mg daily dose level. If dose reduction is needed, at the 15 mg dose level, cediranib should be taken on an empty stomach, at least 1 hour before or 2 hours after a meal. For patients with difficulty swallowing tablets, cediranib tablets may be dispersed in non-carbonated drinking water.

5.4 Screen failures

Please refer to Section 5.4 of the core protocol.

6 STUDY TREATMENTS

Study treatment is defined as any study drug(s) (including marketed product comparator and placebo) or medical device(s) intended to be administered to a study participant according to the study protocol. Study treatment in this Module 7 refers to durvalumab and cediranib.

6.1 Treatments administered

6.1.1 Study drugs

Table 2 Investigational products

	Cediranib	Durvalumab
Dosage formulation:	Supplied as 15 or 20 mg tablets.	Supplied as a vialed liquid solution containing 500 mg (nominal) durvalumab per vial. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine hydrochloride, 275 mM trehalose dihydrate, 0.02% (w/v) polysorbate 80, at pH 6.0. The nominal fill volume is 10.0 mL.
Route of administration:	Oral	IV infusion
Dosing instructions:	Cediranib 20 mg daily. The tablets are to be administered orally on an intermittent schedule (5 days on, 2 days off), starting on Cycle 1 Day 1 for durvalumab. In case of dose reduction, cediranib 15 mg tablets will be used.	Durvalumab 1500 mg via IV infusion Q4W ±2 days (fixed dosing for patients >30 kg bodyweight).
Packaging and labelling:	Study treatment will be provided in bottles. Labels will be prepared in accordance with GMP and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labeling. Label text will be translated into local language, as required. Cediranib will be provided with either single-panel labels or multi-language booklet labels. Specific dosing instructions will not be included on the label; the site must complete the "Patient Dispensing Card" with the details of the dosing instructions at the time of dispensing. The investigator's emergency contact details will not be on the label, but can be found in the informed consent and the 'Patient Dispensing Card'. For emergency purposes the patient must be in possession of the emergency contact details at all times.	Study drug will be provided in vials. Each vial will be labelled in accordance with GMP Annex 13 and per country regulatory requirement. Labels will be prepared in accordance with GMP and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language, as required. Durvalumab will be provided with either single-panel labels or multi-language booklet labels. The investigator's emergency contact details will not be on the label, but can be found in the informed consent and the 'Patient Emergency Card'. For emergency purposes, the patient must be in possession of the emergency contact details at all times.
Provider:	AstraZeneca	AstraZeneca. Commercially available 0.9% (w/v) saline or 5% (w/v) dextrose IV bags will be supplied by each site.

GMP Good Manufacturing Practice; IV intravenous(ly); Q4W every 4 weeks; w/v weight/volume.

6.2 Preparation/handling/storage/accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study drugs received and any discrepancies are reported and resolved before use of the study treatment.

Only patients enrolled in the study may receive study treatment and only authorised site staff may supply or administer study drugs. All study drugs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study drug accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study drug are provided in the Pharmacy Manual.

6.2.1 Durvalumab preparation and handling

Durvalumab will be supplied by AstraZeneca as a 500 mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine hydrochloride, 275 mM trehalose dihydrate, and 0.02% (weight/volume [w/v]) polysorbate 80; it has a pH of 6.0 and a density of 1.054 g/mL. The nominal fill volume is 10.0 mL.

Study drug vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. The vials should be kept in original packaging until use to prevent prolonged light exposure.

The dose of durvalumab for administration must be prepared by the investigator's or site's designated study drug manager using aseptic technique. Total time from needle puncture of the durvalumab vial to the start of administration should not exceed 4 hours at room temperature or 24 hours at 2°C to 8°C (36°F to 46°F). If the final product is stored at both refrigerated and ambient temperatures, the total time should not exceed 24 hours.

A dose of 1500 mg (for patients >30 kg in weight) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab concentration ranging from 1 to 15 mg/mL and delivered through an IV-administration set with a 0.2-µm or 0.22-µm filter. Add 30.0 mL (ie, 1500 mg) of durvalumab to an appropriately sized IV bag such that the final concentration is within 1 to 15 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

If a patient's body weight falls ≤30 kg during the study, (s)he will be withdrawn from the study treatment unless (s)he derives some clinical benefit according to the treating physician. In this

case, and following agreement between the treating physician and the Sponsor, the patient may continue treatment at a body-weight adapted dose of 20 mg/kg actual body weight.

Weight-based dosing at 20 mg/kg (for patients ≤30 kg) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab concentration ranging from 1 to 15 mg/mL, and delivered through an IV administration set with a 0.2-µm or 0.22-µm filter. An example of a weight-based dose calculation is shown in Section 6.2.1.1.

Standard infusion time is one hour (±15 minutes), however if there are interruptions during infusion, the total allowed infusion time should not exceed 8 hours at room temperature.

If either preparation time or infusion time exceeds the time limits a new dose must be prepared from new vials. Durvalumab does not contain preservatives, and any unused portion must be discarded.

Do not co-administer other drugs through the same infusion line.

The IV line will be flushed with a volume of IV diluent equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered.

Durvalumab should be given at least 1 hour after the patient has taken their cediranib morning dose (on cediranib dosing days). Patients will be monitored before, during, and after the first durvalumab infusion with assessment of vital signs at the times specified in the SoA (Table 1) and Section 8.2.3 of the core protocol. If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be at the investigator's discretion (suggested 30 minutes after each durvalumab infusion). For management of patients who experience an infusion reaction, please refer to the toxicity and management guidelines for infusion related reactions.

Durvalumab (1500 mg) will be administered via IV infusion Q4W ± 2 days. Treatment with durvalumab will commence on Day 1 following confirmation of eligibility and will continue on a Q4W schedule until disease progression is confirmed/unacceptable toxicity/withdrawal of consent/other.

6.2.1.1 Durvalumab weight-based calculation

If a patient's body weight falls ≤30 kg during the study, (s)he will be withdrawn from the study treatment unless (s)he derives some clinical benefit according to the treating physician. In this case, and following agreement between the treating physician and the Sponsor, the patient may continue treatment at a body-weight adapted dose of 20 mg/kg of durvalumab Q4W until the

weight improves to >30 kg, at which point the patient should start receiving the fixed dosing of durvalumab 1500 mg Q4W:

1 Cohort dose: X mg/kg

2 Patient weight: Y kg

3 Dose for patient: XY mg = X (mg/kg) × Y (kg)

4 Dose to be added into infusion bag:

Dose (mL) = XY mg/50 (mg/mL) where 50 mg/mL is durvalumab nominal concentration. The corresponding volume of durvalumab should be rounded to the nearest tenth mL (0.1 mL). Dose adjustments for each cycle are only needed for greater than 10% change in weight.

5 The number of vials required for dose preparation is the next greatest whole number of vials from the following formula:
Number of vials = Dose (mL) / 10.0 (mL/vial)

Example:

- Cohort dose: 20 mg/kg
  (a) Patient weight: 30 kg
  (b) Dose for patient: 600 mg = 20 (mg/kg) × 30 (kg)
  (c) Dose to be added into infusion bag:
  Dose (mL) = 600 mg / 50 (mg/mL) = 12.0 mL
  (d) The number of vials required for dose preparation:
  Number of vials = 12.0 (mL) / 10.0 (mL/vial) = 2 vials

6.2.2 Cediranib administration

Patients will take cediranib 20 mg orally every 24 hours on an intermittent schedule (5 days on, 2 days off), in combination with durvalumab at a dose of 1500 mg every 4 weeks via a 60-minute intravenous administration.

For all centres, cediranib will be packed in high-density polyethylene bottles with child-resistant closures. The cediranib study treatment will be dispensed to patients. Multiple bottles of study treatment may be required for dispensing in order to make up the desired dose.

Patients will be administered cediranib study treatment tablets orally at a dose of 20 mg 5 days on, 2 days off. The planned dose of 20 mg od will be made up of 1 × 20 mg tablet 5 days on, 2 days off. The 15 mg tablet will be used to manage dose reductions on an intermittent schedule (5 days on, 2 days off) (see Table 6).

Doses of study treatment should be taken at the same time each morning and can be taken with or without food. For patients with difficulty swallowing tablets, cediranib tablets may be dispersed in water; cediranib tablets may be dispersed by dropping the tablet in 50 mL (approximately half a glass) of non-carbonated drinking water, without crushing, and stirring for 10 minutes, and immediately swallowing this suspension. Any residues left in the glass are to be mixed with another half a glass of water as described above, and then swallowed immediately. If dose reduction is needed, at the 15 mg dose level, cediranib should be taken on an empty stomach, at least 1 hour before or 2 hours after a meal.

If a patient misses a dose, the patient should be advised to take the dose as soon as possible provided this happens within 6 hours of the scheduled time. If it is more than 6 hours after the scheduled time, cediranib should not be taken for that day. Cediranib should be taken as scheduled on the next day. A patient should not take more than a single daily dose on a given day. Patients should not "make up" a missed dose or a dose that was vomited. For dose modification guidance, please see Section 8.4.5.2, Table 6.

6.2.3 Study drug administration

It is important to follow the assessment schedule as closely as possible.

Patients should continue to receive study treatment (ie, durvalumab in combination with cediranib) until objective radiological disease progression as per RECIST 1.1 as long as, in the investigator's opinion, they are benefiting from treatment and they do not meet any other discontinuation criteria. Disease progression should be confirmed by a subsequent scan (no earlier than 4 weeks later) in the absence of clinically significant deterioration as assessed by the investigator. All patients who have objective progression of disease will enter follow-up.

Cediranib dosing must remain aligned to the durvalumab dosing on Day 1 of each cycle; cediranib treatment weeks will always start on Days 1, 8, 15 and 22 of a 4-week cycle.

If durvalumab is delayed, cediranib Day 1 must also be delayed until durvalumab is given.

If cediranib is interrupted, it must not be restarted on planned 'off treatment' days.

If either durvalumab or cediranib treatment is interrupted for more than 3 weeks, the patient should permanently discontinue study treatment unless they have clinical benefit and it is agreed in discussion with the study physician (see also Section 7 of the core protocol).

6.2.4 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. The cediranib product label on the bottle specifies the appropriate storage. Storage is also described in the cediranib IB.

Durvalumab is to be stored at the study centre in a secured facility with limited access and controlled temperature (2°C to 8°C). The temperature should be monitored on a daily basis and documented in the temperature monitoring log according to the study drug handling instructions.

The study drug must be kept in the original outer container and under conditions specified on the labels.

In the following cases, the centre staff should not use affected study drug and should immediately contact AstraZeneca representative for further guidance:

- Temperature excursion upon receipt or during storage at the study
- Damaged kit upon receipt
- Damaged vial/bottle.

Damaged study drug should be documented according to the instructions provided by AstraZeneca representative. Storage conditions stated in the Investigator's Brochure, or the study drug Handling Instructions document, may be superseded by the label storage.

6.2.5 Accountability

The study drugs provided for this study should only be used as directed in the study protocol.

The study site staff will account for all study drugs received at the centre, for unused study drugs, and for appropriate destruction (according to local procedures). Certificates of delivery, destruction, and/or return should be signed.

The administration of all medications (including study drug) and details of treatment with study drug should be recorded in the appropriate sections of the electronic Case Report Form (eCRF).

6.3 Measures to minimise bias: randomisation and blinding

This is an open label study.

Recruitment into the biomarker non-matched arm will be conducted in a sequential manner.

If a patient withdraws from participation in the study, then his/her enrolment code cannot be reused. Withdrawn patients will not be replaced.

6.4 Treatment compliance

The administration of all study drugs should be recorded in the appropriate sections of the eCRF. Durvalumab will be administered on site. Treatment compliance will be assured by reconciliation of site drug accountability logs. Patients will record their oral cediranib dosing on a diary which should be returned to the site at the next available visit. Sites should additionally record cediranib doses taken at site visits.

Patients will self-administer cediranib. Patients should be given clear instructions on how and when to take their study treatment. Study site staff will make tablet counts at regular intervals during treatment. Compliance will be assessed by the tablet count and the information will be recorded in the appropriate section of the eCRF. After the tablet count has been performed, the remaining tablets will not be returned to the patient but will be retained by the investigative site until reconciliation is completed by the study physician. All patients must return their bottle(s) of cediranib at the appropriate scheduled visit, when a new bottle will be dispensed. Patients will be instructed to notify study site personnel of missed doses. Dates of missed or held doses will be recorded by the patient on their patient diary and by the site staff on the eCRF.

Patients must return all containers and any remaining tablets at the end of every cycle to indicate compliance.

Any change from the dosing schedule, dose interruptions, dose reductions, dose discontinuations should be recorded in the eCRF. Note: Dose reductions are not allowed for durvalumab.

The Study Drug Storage Manager is responsible for managing the study drug from receipt by the study site until the destruction or return of all unused study drug. The investigator(s) is/are responsible for ensuring that the patient has returned all unused study drug.

Use of study treatment in doses in excess of that specified in the protocol (5 days on 2 days off for cediranib) is considered to be an overdose. Refer to Section 8.4.3 for procedures in case of overdose.

6.5 Concomitant therapy

Any medication or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the patient received in the 4 weeks prior to starting study treatment, is receiving at the time of enrolment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency.

If medically feasible, patients taking regular medication other than those excluded from this study should be maintained on it throughout the study period.

Prohibited concomitant medications are described in Table 3. Please refer to Section 8.4.5 for guidance on management of study drug-related toxicities.

The use of concomitant medications must be recorded in the eCRF.

Table 3 Prohibited medications

Prohibited medication/class of drug:	
Unless stated otherwise, these medications are prohibited from the time that patients enter the main screening period until the last dose of study treatment. The pre-screen may be done whilst on prior therapy.	
Any investigational anticancer therapy other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment
Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment. (Note: concurrent use of hormones for non-cancer-related conditions [eg, insulin for diabetes and hormone replacement therapy] is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable [eg, by local surgery or radiotherapy]). Patients may receive treatment with bisphosphonates or RANKL inhibitors for the treatment of bone metastases.
Immunosuppressive medications, including, but not limited to: systemic corticosteroids at doses exceeding 10 mg/day of prednisone or its equivalent, methotrexate, azathioprine, and tumour necrosis factor-α blockers	Should not be given concomitantly, or used for premedication prior to the infusions. The following are allowed exceptions: • Use of immunosuppressive medications for the management of study drug-related AEs • Short-term premedication for patients receiving combinations where the prescribing information for the agent requires the use of steroids for documented hypersensitivity reactions • Use in patients with contrast allergies • In addition, use of inhaled, topical, and intranasal corticosteroids is permitted. A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of non-immunotherapy related events experienced by the patient (eg, chronic obstructive pulmonary disease, radiation, nausea, etc).
Live attenuated vaccines	Prohibited from the time that patients enter the main screening period until 180 days after the last dose of study treatment.
Epidermal growth factor receptor (EGFR) Other tyrosine kinase inhibitors (TKIs), other than cediranib	Should not be given concomitantly. Should be used with caution in the 90 days post last dose of durvalumab. Increased incidences of pneumonitis (with third generation EGFR TKIs) and increased incidence of transaminase increases (with 1st generation EGFR TKIs) have been reported when durvalumab has been given concomitantly.
Herbal and natural remedies which may have immune-modulating effects	Should not be given concomitantly unless agreed by the sponsor

AE adverse event

The use of herbal preparations/medications should be discouraged throughout the study. These herbal medications include, but are not limited to: St. John's Wort, kava, ephedra (ma huang),

gingko biloba, dehydroepiandrosterone, yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 7 days prior to first dose of study drug (3 weeks for St John's Wort). Use of these products, as well as use of all vitamins, nutritional supplements and all prescribed concomitant medications, must be recorded in the eCRF.

Other concomitant treatment

Patients who begin warfarin therapy should be advised to have their anticoagulation monitored more frequently when receiving cediranib and should stop medication with cediranib if the patient develops CTCAE Grade ≥3 thrombocytopenia (see also Section 6.5.2).

Patients may continue to receive therapeutic bisphosphonates or denosumab and erythropoietin preparations (Procrit®, Epogen®, Aranesp®), if they were receiving them prior to beginning study treatment.

Blood transfusions are allowed during the study.

Caution should be exercised in the concomitant use of any medication that may markedly affect renal function. Such medications may be used with caution as deemed essential for treatment, or if already in use prior to study entry without any effect on renal function.

Medication other than that described above, which is considered necessary for the patient's safety and wellbeing, may be given at the discretion of the investigator and recorded in the appropriate sections of the eCRF.

6.5.1 Rescue and supportive medication

The study site will supply rescue medication and this will be procured locally. The sponsor will supply only if required by local regulations.

The use of rescue medications is allowable at any time during the study. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

Supportive medication, described in Table 4, may be given at the discretion of the investigator and recorded in the appropriate sections of the eCRF.

Table 4 Supportive medication

Supportive medication/class of drug:	Usage:
Concomitant medications or treatments (eg, acetaminophen or diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care, except for those medications identified as "prohibited," as listed above	To be administered as prescribed by the investigator
Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy to non-target lesions, etc])	Should be used, when necessary, for all patients
Inactivated viruses, such as those in the influenza vaccine or authorised and approved COVID-19 vaccines	Permitted Administration of COVID-19 vaccines should be avoided for 72 hours prior to administration of the first dose of study treatment.

COVID-19 Coronavirus Disease 2019.

6.5.2 Effect of cediranib on other drugs

Cediranib and inducers of PgP/UGT

In vitro data indicate that cediranib is unlikely to cause interactions with CYP450 inducers, inhibitors, and substrates. Cediranib oxidative metabolism appears to be mediated by flavin containing monooxygenase enzymes FMO1 and FMO3 and glucuronidation by UGT1A4. Co-administration of cediranib with strong inducers of PgP/UGT decrease cediranib plasma concentrations; therefore, use of potent inducers of UGT/PgP (eg, rifampicin, carbamazepine, phenobarbital, phenytoin and St. John Wort) should be avoided if possible. Cediranib is a substrate of MDR1 (Pgp), and possible substrate of BCRP. Cediranib is not an inhibitor of OAT1 and OAT3, but it has a low potential to inhibit MDR1 (Pgp), BCRP, OATP1B1, OATP1B3, OCT2, MATE1. The clinical impact of this finding is unknown. Cediranib may act as an inhibitor of renal tubular MATE2-K, this could increase exposure of co-administered agents such metformin or to endogenous agents such as creatinine; however, the ICON6 study showed that increases of blood creatinine caused by 20 mg/day cediranib treatment were infrequent (4.4%) and only mild in severity, suggesting the clinical impact of renal tubular MATE2-K inhibition by cediranib is small.

Anticoagulant therapy

Patients who are taking warfarin may participate in this trial; however, it is recommended that prothrombin time (International Normalized Ratio [INR] and activated partial thromboplastin time) be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Subcutaneous heparin and low molecular weight heparin are permitted.

Palliative radiotherapy

Palliative radiotherapy may be used provided the investigator does not feel that the need for radiation is not indicative of clinical disease progression during the study period (see Appendix G4.2 of the core protocol). Cediranib should be discontinued for a minimum of 3 days before a patient undergoes therapeutic palliative radiation treatment. Cediranib should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.

6.5.3 Hypertension medication

The anti-hypertensive medications in Table 5 have been provided as a guide and those used in this study will depend upon local practice.

Note: Agents in bold characters are suggested as optimal choices to avoid or minimise potential drug-interactions with cediranib through cytochrome P450 (CYP450).

Table 5 Hypertension medication

Agent	Initial dose	Intermediate dose	Maximum dose	Hepatic metabolism?
Dihyropyridine calcium channel blockers				
Nidefipine XL	30 mg po od	60 mg po od	90 mg po od	CYP3A4 substrate
Amlodipine	2.5 mg po od	5 mg po od	10 mg po od	CYP3A4 substrate
Felodipine	2.5 mg po od		10 mg po od	CYP3A4 substrate + inhibitor
Selective beta blockers				
Metoprolol	25 mg po bid	50 mg po bid	100 mg po bid	CYP2D6 substrate
Atenolol	25 mg po od	50 mg po od	100 mg po od	No
Acebutolol	100 mg po bid	200-300 mg po bid	400 mg po bid	Yes (CYP450 questionable)
Bisoprolol	2.5 mg po od	5-10 mg po od	20 mg po od	Yes (CYP450 questionable)
Angiotensin converting enzyme inhibitors				
Captopril	12.5 mg po tid	25 mg po tid	50 mg po tid	CYP2D6 substrate
Enalapril	5 mg poo	10-20 mg po od	40 mg po od	CYP3A4 substrate
Ramipril	2.5 mg po od	5 mg po od	10 mg po od	Yes (CYP450 questionable)
Lisinopril	5 mg po od	10-20 mg po od	40 mg po od	No
Fosinopril (rarely used)	10 mg po od	20 mg po od	40 mg po od	Yes (CYP450 questionable)
Perindopril	4 mg po od	none	8 mg po od	Yes, but not per CYP450
Quinapril	10 mg po od	20 mg po od	40 mg po od	No
Angiotensin II receptor blockers				
Losartan	25 mg po od	50 mg po od	100 mg po od	CYP3A4 substrate
Candesartan	4 mg po od	8-16 mg po od	32 mg po od	CYP2C9 substrate
Irbesartan	75 mg po od	150 mg po od	300 mg po od	CYP2C9 substrate
Telmisartan	40 mg po od	None	80 mg po od	Yes, but not per CYP450
Valsartan	80 mg po od	None	160 mg po od	Yes, but not per CYP450
Alpha and beta blocker				
Labetolol	100 mg po bid	200 mg po bid	400 mg po bid	CYP2D6 substrate + inhibitor

bid twice daily; CYP cytochrome P450; od once daily; po orally; tid three times daily

6.6 Dose modification and discontinuation

For patients who weigh >30 kg, the dose of durvalumab cannot be modified. If a patient's body weight falls ≤30 kg during the study, (s)he will be withdrawn from the study treatment unless (s)he derives clinical benefit according to the treating physician. In this case, and following agreement between the treating physician and the Sponsor, the patient may continue treatment at a body-weight adapted dose of 20 mg/kg actual body weight.

Durvalumab dosing can be temporarily discontinued in the event of treatment-related toxicity. All toxicities will be graded according to Common Toxicity Criteria for Adverse Events (CTCAE) version 4.03. Dose reductions are not permitted. In case of doubt, the investigator should consult with the study physician. Please refer to the toxicity management guidelines for durvalumab.

Dose reductions or interruptions of cediranib, and initiation of supportive care, are allowed as deemed appropriate by the treating physician, per the toxicity management guidelines (Section 8.4.5). The maximum interruption that is permitted is 3 weeks. Any patient requiring a toxicity related dose delay of more than 3 weeks from the intended day of the next scheduled dose must be discontinued from the study unless the patient is deriving clinical benefit and there is approval from the Study Physician for the patient to continue.

Dose reduction and discontinuation guidelines for toxicities for cediranib are shown in Section 8.4.5.2 and dose modification guidance can be discussed with the study physician if investigators wish to deviate from the guidance based on their medical assessment.

Cediranib can be dose reduced to 15 mg (5 days on/2 days off) (Table 6). If the reduced dose of 15 mg is not tolerable, no further dose reduction is allowed and study treatment should be discontinued. Once the dose is reduced, escalation is not permitted. In order to reduce the dose, new tablets will need to be dispensed.

6.7 Treatment after the end of the study

Patients are permitted to either receive standard of care therapy, or to continue to receive study treatment following the end of the study if, in the opinion of the investigator, they are continuing to receive benefit from treatment. After discontinuation of study treatment, the investigator will be at liberty to define further most appropriate anti-cancer treatment. Subsequent anti-cancer treatment is expected to be initiated following the cancer recurrence or development of a new cancer. Information on subsequent anti-cancer therapies should be recorded on the clinical database.

7 DISCONTINUATION OF TREATMENT AND SUBJECT WITHDRAWAL

Please refer to Section 7 in the core protocol.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in the SoA (Table 1).

8.1 Efficacy assessments

Please refer to the core protocol.

8.2 Safety assessments

8.2.1 Clinical safety laboratory assessments

Please refer to core protocol for the standard laboratory assessments.

Urinary protein/creatinine (UPC) ratio is required in addition to the standard laboratory assessments.

8.2.1.1 Coagulation

Please refer to core protocol. For patients taking warfarin, see also Section 6.5.2 of this module.

8.2.1.2 Other safety assessments

Please refer to core protocol.

8.2.1.3 Pneumonitis (interstitial lung disease) investigation

The following assessments, and additional assessments if required, will be performed to enhance the investigation and diagnosis of potential cases of pneumonitis. The results of the assessment will be collected.

- Physical examination; Signs and symptoms (cough, shortness of breath and pyrexia, etc) including auscultation for lung field will be assessed.
- SpO_2; Saturation of peripheral oxygen (SpO_2)
- Other items; When pneumonitis (interstitial lung disease [ILD]) is suspected during study treatment, the following markers should be measured where possible:
  - ILD Markers (KL-6, SP-D) and β-D-glucan
  - Tumour markers: Particular tumour markers which are related to disease progression.

8.2.1.4 Urinalysis

In addition to the standard laboratory assessments in the core protocol, urine samples must be collected at Screening, on Cycle 1 Day 1, Cycle 1 Day 15, and Day 1 of each subsequent cycle, and drug discontinuation (Table 1) to monitor for proteinuria. For proteinuria assessment follow instructions in Table 9.

Patients with urine protein ≥3.5 g/24 hours (CTCAE Grade 3 according to CTCAE v4.03) or UPC ratio of >3.5 should be considered as nephrotic-range proteinuria. See Table 9 for dosing guidance in managing proteinuria.

Following identification of nephrotic range proteinuria, the following steps should be taken to explore if the patient has a nephrotic syndrome:

- Confirm if the patient had a normal renal function at baseline (creatinine ≤ULN)

- Check if the patient has reported any of the following as a treatment-emergent and concurrent AE: hypoalbuminemia (laboratory value albumin <3 g/dL, or an AE of hypoalbuminemia CTCAE Grade ≥2); oedema (any); dyslipidaemia (hypercholesterolemia, hypertriglyceridemia); hyperlipidaemia; or a thrombotic event.

8.2.2 Physical examinations

Please refer to core protocol.

8.2.3 Vital signs

Please refer to core protocol for the standard vital signs assessments. Additional blood pressure assessments are required in Module 7.

All patients should check their BP twice daily for at least the first 8 weeks after starting study drugs, or, if antihypertensive management is required, until a stable anti-hypertensive regimen has been established overall for at least 8 weeks and even if this requires more than 8 weeks. After 8 weeks or once a stable regimen has been achieved (per the Investigator's judgement), BP monitoring may be reduced to once daily. Twice daily monitoring should be re-implemented after any cediranib dose interruption for at least 2 weeks or until the patient is re-established on a stable antihypertensive regimen, whichever takes longer. Patients should continue to check their BP for as long as they remain on cediranib treatment and for 30 days after cediranib discontinuation. Patients will record their BP and pulse rate data using handheld electronic devices, to be provided by the study Sponsor, and the Sponsor is expected to have a knowledge of the blood pressures reported by the patients at home.

Patient BP will also be measured during routine study visits to ensure that BP guidelines are being correctly followed. During routine study visits, BP and pulse rate will be measured preferably using a semi-automatic BP recording device with an appropriate cuff size after 10 minutes rest. For timings of assessments refer to the SoA (Table 1). The Investigator will also need to review the home registered BP and pulse prior to taking the vital signs of the patient during the visit.

Patients should seek medical advice of their treating physician if their BP exceeds 160 mmHg (systolic) or 100 mmHg (diastolic) at any time and should also contact their treating physician if they are concerned about any symptoms that may be associated with high blood pressure (eg, headache). Section 8.4.5.2 includes specific guidelines on the management and, if appropriate, dose modifications for treatment-emergent hypertension.

8.2.4 Electrocardiograms

Please refer to core protocol.

8.2.5 Echocardiogram or MUGA

ECHO or MUGA should be conducted at the timepoints indicated in the SoA (Table 1) and as clinically indicated while on study (Section 8.4.5.2 and Table 11).

8.2.6 Performance status

Please refer to core protocol.

8.3 Collection of adverse events

Please refer to the core protocol.

8.4 Safety reporting and medical management

8.4.1 Reporting of serious adverse events

Please refer to the core protocol.

8.4.2 Pregnancy

Please refer to the core protocol.

8.4.3 Overdose

Please refer to the core protocol for information on durvalumab-related overdose.

A dose of cediranib in excess of that specified according to the protocol will constitute an overdose, ie,:

- Cediranib dose taken > the daily planned dose
- Cediranib has been taken for > 5 daily doses in any 7 days.

If patients meet either of the criteria above for an overdose, it should be reported on the appropriate section of the eCRF (Section 6.4).

Approximately 290 patients have received cediranib at dose levels of 45 mg or higher. At these higher dose levels the cediranib safety profile was similar to that observed at lower dose levels of 20 mg. In cases of suspected overdose, cediranib should be paused, BP monitored and if needed, supportive care instituted. There is no specific treatment for cediranib overdose. At the discretion of the Investigator, re-starting cediranib at the recommended dose can be considered.

8.4.4 Medication error

Please refer to the core protocol.

8.4.5 Management of study-drug related toxicities

At this time, there are limited safety data regarding the combination of durvalumab and cediranib. Given the differing mechanisms of action of durvalumab and cediranib, the potential for potentiation of toxicities is thought to be limited. Some toxicities, for example hyperthyroidism and asthenia/fatigue may, on theoretical grounds, be potentiated in the combination arm and particular attention should be paid to these.

In the event of toxicity in this combination arm of the study which cannot be managed by supportive measures alone, stopping one or both medications should be an investigator decision based on the available information and, if necessary, following discussion with the sponsor.

The following general guidance should be followed for management of toxicities:

- Treat each of the toxicities with maximum supportive care (including withholding the agent suspected of causing the toxicity if required).
- If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of the assigned study drug along with appropriate continuing supportive care. If medically appropriate, 1 dose modification is permitted for cediranib. In addition, guidelines on cediranib dose modifications are provided in Section 8.4.5.2. In the event of toxicity that cannot be managed by following the toxicity management guidelines for cediranib and durvalumab, consider stopping treatment with cediranib or durvalumab depending on which agent is mostly implicated in the AE.

All dose modifications should be documented with clear reasoning and documentation of the approach taken. Dose reductions are not permitted without prior agreement with the study physician.

8.4.5.1 Management of durvalumab-related toxicities

Please refer to the toxicity management guidelines for durvalumab.

8.4.5.2 Management of cediranib-related toxicities

Patients receiving the combination of durvalumab plus cediranib may report AEs that are known to be associated with cediranib alone. Management guidelines for such AEs are provided below.

Management of cediranib-related toxicities in general

The dose levels and the general approach to dose modification of cediranib is shown in Table 6. Specific dose modification information for some AEs is provided in the relevant section below. AEs should be treated with the appropriate maximum supportive care, and dose reductions should be clearly documented in the eCRF.

Table 6 Recommended dose reductions for cediranib

Dose level	Cediranib monotherapy dose (5 days on, 2 days off)
Initial dose	20 mg for 5 days on, 2 days off
Dose reduction 1	15 mg for 5 days on, 2 days off

NB: The dose of durvalumab is 1500 mg, given by a 60-minute infusion every 4 weeks. There are no dose reductions for durvalumab in this study.

At the discretion of the investigator, the study drug may be withheld or dose modified (as specified in the sections below). Dosing weeks need to remain aligned to the durvalumab dosing on Day 1 of each cycle (see Section 6.2.3). The time the drug is withheld should not exceed 3 weeks. Once the dose of study drug has been reduced, no dose re-escalation is permitted.

AEs requiring cediranib to be discontinued:

- GI perforation
- Arterial thromboembolic event
- PRES
- Severe haemorrhage
- Severe persistent hypertension despite maximal anti-hypertensive treatment.

Management of cediranib-associated toxicities

Hypertension

In clinical trials, increases in blood pressure have been reported within a few hours of starting cediranib. Since rapid changes in blood pressure can occur with cediranib treatment, with the potential for life-threatening complications if hypertension is not appropriately managed, all patients should check their blood pressure twice daily for at least the first 8 weeks after starting cediranib, or, if antihypertensive management is required, until a stable anti-hypertensive regimen has been established, overall for at least 8 weeks and even if this requires more than 8 weeks. After 8 weeks or once a stable regimen has been achieved, blood pressure monitoring may be reduced to once daily. Twice daily monitoring should be re-implemented after any cediranib dose interruption for 2 weeks or until the patient is re-established on a stable antihypertensive regimen, whichever takes longer.

Patient blood pressure will also be measured during routine study visits, after the Investigator has checked the home measured results, to ensure that blood pressure guidelines are being correctly followed. Increase in blood pressure observed during routine study visits, or from the patient's BP measurements at home should be treated promptly with standard antihypertensive therapy, ensuring that the maximum recommended dose and number of antihypertensive medicinal products is reached before considering cediranib dose adjustment. See Section 6.5.3 for

suggested antihypertensive medications by class. Patients may have up to 4 drugs for management of hypertension prior to any dose reduction in cediranib.

If patient has combined systolic (> 160 mm Hg) and diastolic (> 100 mm Hg) hypertension for > 7 days in a row, which is new in onset (subject not known previously to have hypertension) or not controlled by optimising the subject's baseline anti-hypertensives regimen (for subjects with known hypertension), a dose reduction will need to be applied (see Table 6).

If patients require a delay of >3 weeks for management of hypertension, discontinuation of cediranib or protocol therapy may be considered after discussion with the Investigator and the AstraZeneca study physician. In case of persistent or severe hypertension, despite the optimal use of antihypertensive medicinal products and cediranib dose reduction, cediranib should be permanently discontinued.

Patients already taking antihypertensive therapy at baseline or those aged 75 years or older are at a higher risk of having elevated blood pressure or may require more than one medicinal product or more intensive therapy. Pre-existing cardiovascular risks should be assessed and managed, and pre-existing hypertension should be adequately controlled before starting treatment with cediranib. Note: Stopping or reducing the dose of cediranib is expected to cause a decrease in blood pressure. The treating physician should monitor the patient for hypotension and adjust the number and dose of antihypertensive medications accordingly.

Hypertension should be graded using the NCI CTCAE. Please note: patients may have baseline hypertension meeting CTCAE grading criteria on study entry provided this is adequately controlled on maximum of 3 antihypertensive medications.

Baseline grade of hypertension should also be recorded in the Medical History eForm. Should patients require increase in dosing of BP medication or increased number of medications, they should then be noted to have hypertension related to study drug, with grading as per CTCAE criteria.

Table 7 provides hypertension monitoring and management guidance.

Table 7 Hypertension monitoring and management

Event	Definition	Antihypertensive therapy	Blood pressure monitoring	Cediranib dose modification [a]
Grade 1	Asymptomatic transient (<24 h) increase by >20 mmHg diastolic or to >140/90 mmHg if previously within normal limits	Consider early initiation of BP medication for BP >140/90 mmHg that is confirmed on a second reading. Cediranib can cause rapid escalation in BP, and early initiation of BP management can reduce likelihood of hypertension-related complications.	Continue standard BP monitoring according to local practice and confirm resolution of BP to <140/90 mmHg within 24 h.	None
Grade 2	Recurrent or persistent (>24 h) or symptomatic increase by >20 mmHg (diastolic) or to >140/90 mmHg if previously within normal limits Monotherapy may be indicated	Initiate BP medication for first line treatment: *Suggestion:* ACE inhibitor or calcium channel blocker Escalate dose of medication in step wise fashion until BP is controlled or at a maximum dose If BP is not controlled to <140/90 mmHg with one "maximised" drug regimen, then add a second agent: Study drug does not need to be held unless otherwise clinically necessary *Consider renal consult*	Increase frequency of monitoring until stabilized to BP <140/90 mmHg	Do not hold cediranib unless otherwise clinically necessary

Table 7 Hypertension monitoring and management

Event	Definition	Antihypertensive therapy	Blood pressure monitoring	Cediranib dose modification [a]
Grade 3	Requiring more than 1 drug or more intensive therapy than previously.	Maximise 2 drug regimen *Suggestions:* ACE inhibitor + calcium channel blocker Escalate doses of existing medication until BP is controlled or at a maximum dose. If BP is not controlled to <140/90 mmHg with 2 drug regimens, then add a third agent. Study drug will not be held during trial of 2 drug combinations. Additional antihypertensive drugs, up to a total of 4, may be maximized for BP control. *Consider consult with a BP management specialist if greater than 3 drugs are required for BP control.*	Increase frequency of monitoring until stabilised to BP <140/90 mmHg	Do not hold cediranib unless BP is not decreased to less than 150/100 mmHg 48 hours after multi-drug therapy is instituted or if clinical symptoms worsen (eg, headache). If BP is not controlled to less than 150/100 mmHg with maximal therapy or if clinical symptoms worsen, then hold drug (up to 3 weeks) until maximum effect of the antihypertensive agents is achieved. If BP is reduced to Grade 1 within 3 weeks, cediranib may be resumed at prior dose.
Grade 4	If threatening consequences **OR** SBP ≥180 mmHg **OR** DBP ≥110 mmHg	Initiate treatment Hospitalise patient for ICU management, IV therapy as necessary 14 days are allowed to maximise the full effect of antihypertensive agents.	Intensive BP monitoring (hospitalisation if necessary)	Withhold cediranib. If BP is reduced to Grade 1 within 3 weeks, cediranib may be resumed at a reduced dose after discussion with the PI

[a] If a patient has combined systolic (>160 mm Hg) and diastolic (>100 mm Hg) hypertension for > 7 days in a row, which is new in onset (subject not known previously to have hypertension) or not controlled by optimising the subject's baseline anti-hypertensives regimen (for subjects with known hypertension), a dose reduction will need to be applied (see Table 6)

ACE angiotensin converting enzyme; BP blood pressure; DBP diastolic blood pressure; ICU intensive care unit; IV intravenous; SBP systolic blood pressure

Diarrhoea

Diarrhoea is often observed with cediranib. Diarrhoea usually starts early (within the first 4 weeks of treatment), however, it can occur at any time during treatment. Management of diarrhoea should start at the first sign of diarrhoea. Loperamide and advice on how to manage

diarrhoea should be readily available to patients from the start of cediranib treatment so that they can be applied at first episode of diarrhoea. Active and early management of diarrhoea is recommended even with Grade 1 diarrhoea. Management is as shown in Table 8.

Table 8 Management of diarrhoea

Toxicity	Management/Modifications
Initial Grade 1 or 2 diarrhoea	Patients should start loperamide (per standard practice) and continue to take loperamide until patients are free from diarrhoea for at least 12 hours. The dose of loperamide should not exceed 16 mg in a 24-hour period. Patients should also be counselled to start a BRAT diet. If diarrhoea persists despite 24 hours of loperamide treatment, withhold cediranib for a maximum of 7 days, continue loperamide, and maintain hydration. Cediranib may be restarted at the same dose once patients have been free from diarrhoea for 12 hours. Patients should be instructed to contact their study physician if mild or moderate (NCI CTCAE Grade 1 or 2) diarrhoea persists for over 48 hours despite treatment with loperamide and cediranib dose interruption.
For either persistent Grade 2 diarrhoea or Grade 3 or 4 diarrhoea	Patients with persistent or severe diarrhoea (NCI CTCAE Grade 3 or higher) may also require dose reduction or discontinuation of therapy with cediranib, follow guidance in Table 6. If immune-mediated diarrhoea is suspected, please see the durvalumab toxicity management guidelines

BRAT bananas, rice, apple sauce, toast; CTCAE Common Terminology Criteria for Adverse Event; NCI National Cancer Institute

Fatigue

Fatigue is a common adverse drug reaction reported for cediranib. Fatigue experienced by patients taking cediranib may be rapid in onset. During clinic visits, patients fatigue levels should be discussed. Patients should seek medical advice early if Grade 2 fatigue develops (moderate fatigue causing difficulty performing some activities of daily living).

Care should be taken to ensure that the nutritional status of the patients is optimised and patients should be encouraged to drink plenty of fluids. Patients should be encouraged to manage fatigue by alternating periods of rest with light aerobic exercise, which may improve the symptoms in some cases.

Consideration should be given to other possible causes of fatigue (eg, thyroid function, depression/insomnia and other concomitant medicinal products). Additionally, short interruption of cediranib dosing (initially 2-3 days-or longer-up to a maximum of 21 days) may help relieve

fatigue. When symptoms improve cediranib should be restarted with the same dose or, if necessary, a dose reduction can be considered.

Proteinuria

Proteinuria is a common adverse reaction reported for cediranib and if this occurs during treatment, it should be managed according to Table 9. For management of suspected cases of nephrotic syndrome, see Section 8.2.1.4.

Table 9 Management of proteinuria

Proteinuria value if following by U/A	Value monitoring	Dose modification
Greater than 2+ on urine dipstick or urinalysis **AND** creatinine ≤1.5x ULN	Perform UPC	Continue study drugs at planned dose.
Greater than 2+ on urine dipstick or U/A **AND** creatinine >1.5x ULN	Perform UPC	Interrupt cediranib until results of UPC are known (see below)
Based on the results of the UPC[a]:		
UPC ≤1.0	Continue monitoring according to schedule of assessments	Continue study drugs at planned dose.
UPC >1.0 and ≤3.5 **AND** creatinine ≤1.5x ULN	Perform UPC at each routine visit.	Continue study drugs at planned dose.
UPC >3.5 **OR** creatinine >1.5x ULN	Perform UPC at each routine visit	Interrupt cediranib for up to 21 days and repeat UPC and creatinine assessment. If UPC resolves to <3.5 and creatinine to ≤1.5x ULN, resume cediranib with reduction in cediranib by one dose level. Consider consultation with nephrologist.

[a] If UPC is <1.0 and creatinine >1.5x ULN, AE management should be followed as above

U/A urinalysis; ULN upper limit of normal; UPC urine protein:creatinine ratio

Management of thyroid toxicities

The use of cediranib has been associated with elevations of TSH and patients should be managed as per Table 10. In all cases, IPs should continue unless clinically contraindicated. Referral to an endocrinologist should also be considered if thyroid abnormalities occur.

Table 10 Monitoring and management of thyroid toxicities

Result of TSH and FT4	Action
Increases of TSH with normal FT4	Monitor
Increases in TSH with normal FT4 and adverse events suggestive of incipient hypothyroidism	Consider replacement thyroxine
Increase in TSH with reductions in FT4	Consider replacement thyroxine

FT4 free thyroxine; TSH thyroid stimulating hormone

Decreased LVEF

Patients who have any of the following should undergo an echocardiogram or MUGA at baseline and as clinically indicated while on study:

- Prior treatment with anthracyclines
- Prior treatment with trastuzumab
- Prior central thoracic radiation therapy (RT), including RT to the heart
- History of myocardial infarction within the prior 6 to 12 months or history of other significant impaired cardiac function (patients with history of myocardial infarction within 6 months are excluded from the study).

The decision to continue or hold cediranib is based on the LVEF as it relates to the institution's lower limit of normal (LLN) and change in ejection fraction from screening (LVEF as measured at registration) according to Table 11.

Table 11 Management and monitoring of decreased LVEF

Relationship of LVEF to Institution's LLN	LVEF Decrease <10%	LVEF Decrease 10% to 15%	LVEF Decrease >15%
Normal	Continue	Continue	Continue and repeat MUGA/ECHO within 4 to 8 weeks
1% to 5% below LLN	Continue and repeat MUGA/ECHO within 4 to 8 weeks	Continue and repeat MUGA/ECHO within 4 to 8 weeks	Interrupt cediranib and repeat MUGA/ECHO within 3 weeks
>6% below LLN	Continue and repeat MUGA/ECHO within 4 to 8 weeks	Interrupt cediranib and repeat MUGA/ECHO within 3 weeks	Interrupt cediranib and repeat MUGA/ECHO within 3 weeks

ECHO echocardiogram; LLN lower limit of normal; LVEF left ventricular ejection fraction; MUGA multigated acquisition scan

Posterior reversible encephalopathy syndrome (PRES)

PRES has been uncommonly reported in clinical studies with cediranib. PRES is a neurological disorder which can present with headache, seizure, lethargy, confusion, blindness and other

visual and neurologic disturbances, and can be fatal. Mild to severe hypertension may be present. In patients developing PRES, treatment of specific symptoms including control of BP is recommended. Confirmation of PRES requires brain imaging, preferably MRI. Cediranib should be discontinued following confirmation of PRES.

Gastrointestinal perforation

Gastrointestinal perforation has been uncommonly reported in cediranib treated patients and may be fatal. Cediranib should be used with caution in patients at risk and permanently discontinued in patients who develop gastrointestinal perforation.

Fistula

In patients treated with cediranib, fistula has been reported and reflected the location of the underling malignancy. In the ovarian cancer population, vaginal fistula has been uncommonly reported in cediranib treated patients. Cediranib should be used with caution in patients at risk of fistula and discontinuation of cediranib should be considered in patients who develop fistulae.

Arterial thromboembolism

Arterial thromboembolic events (including transient ischemic attack and ischemic stroke) have been reported in clinical studies with cediranib. Cediranib should be used with caution in patients who are at an increased risk of thrombotic events or who have a history of thrombotic events. Cediranib should be permanently discontinued in patients who develop an arterial thromboembolic event.

Venous thromboembolism

Venous thromboembolic events including pulmonary embolism and deep vein thrombosis have been commonly reported in patients treated with cediranib. Anticoagulant treatment should be started in accordance with clinical practice. Discontinuation of cediranib may be considered. Cediranib should be used with caution in patients at risk of venous thromboembolism.

Wound healing

Treatment with cediranib should be stopped at least 2 weeks prior to scheduled surgery. The decision to resume cediranib therapy after surgery should be based on clinical judgment of adequate wound healing. In patients who experience wound healing complications during therapy, treatment with cediranib should be interrupted until the wound is fully healed. No formal studies of the effect of cediranib on wound healing have been conducted; however, in the ICON6 pivotal study there was no evidence of an increase in wound healing complications in cediranib treated patients compared with placebo.

Haemorrhage

VEGF inhibition is associated with increased risk of bleeding and haemorrhage. Bleeding/haemorrhagic events have been very commonly reported in cediranib-treated patients. Cediranib should be permanently discontinued in patients who have severe haemorrhage, ie, requiring medical intervention.

Elderly

There is a limited amount of safety data available for cediranib use in patients aged 75 years and older. Based on a population PK analysis, the clearance of cediranib decreased with age, however, no dose adjustment is needed given the small impact on exposure or variability. Caution should be taken when treating patients who are aged 75 years or older with cediranib. In case of toxicity dose pause or dose reduction may be considered.

Mild/moderate renally impaired patients

Patients with mild and moderate renal impairment discontinued cediranib more often due to adverse events, particularly when cediranib was co-administered with chemotherapy. Population PK analysis showed that no adjustment of cediranib dose is required in this population as cediranib is minimally renally cleared; however, cediranib clearance may be decreased in patients with low body weight. In the ICON6 pivotal study, patients with mild or moderate impairment had lower median body weight compared with patients with normal renal function. Caution should be exercised in patients with mild and moderate renal impairment and a cediranib dose adjustment should be considered in case of signs of toxicity.

Weight decreased

In the ICON6 study, weight decreased was very commonly reported in cediranib-treated patients. Weight loss (≥7%) in cediranib-treated patients was associated with higher incidence of decreased appetite, vomiting and stomatitis, although these events were also commonly reported in patients who did not lose weight.

8.4.5.3 Management of shared toxicities of cediranib and durvalumab

The safety profiles of durvalumab and cediranib have been subject to internal evaluation by AstraZeneca. The evaluation revealed that there is limited potential for potentiation of the known adverse drug reactions of both agents, due to the different pharmacological mechanisms of action. The 2 agents have some ADRs in common, eg, diarrhoea, rash (including rash of infusion-related reactions), hyper/hypothyroidism, fatigue and hepatic toxicity, and there is a potential for an increased risk of these overlapping toxicities. Patients in this module will be closely monitored for these such treatment-emergent events.

In the event of toxicity in the combination arm of the study that cannot be managed by supportive measures alone, consider stopping or reducing the dose of cediranib. The recommended dose reductions for cediranib are presented in Table 6.

Toxicity management guidelines for combination therapy (durvalumab plus cediranib)

Specific management guidelines for AEs that are associated with both cediranib and durvalumab, such as diarrhoea, and fatigue should be managed according to the guidelines provided.

The general guidance in Section 8.4.5 should be followed for management of toxicities:

In addition, the following are recommended:

- Patient evaluation to identify any alternative aetiology.
- In the absence of a clear alternative aetiology, all events of an inflammatory nature should be considered to be immune-related and providers should refer to the durvalumab toxicity management guidelines for management of immune-mediated AEs.

8.4.6 Adverse events of special interest for cediranib

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the study drug and may require close monitoring. AESIs may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterise and understand them in association with the use of this study drug.

The AESIs for durvalumab are summarised in core protocol Section 8.3.12.

The AESIs for cediranib are: PRES, arterial thromboembolic events, symptomatic left ventricular dysfunction and cardiac failure; nephrotic syndrome; renal thrombotic microangiopathy and liver failure. Further information on cediranib AESIs is provided in the Investigator's Brochure.

8.5 Pharmacokinetics

Please refer to the core protocol and Table 1.

8.6 Pharmacodynamics

Pharmacodynamic parameters will be evaluated in this study (see Section 8.6 of the core protocol).

8.7 Genetics

Please refer to the core protocol.

8.8 Biomarkers

Please refer to the core protocol.

8.9 Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9 STATISTICAL CONSIDERATIONS

Please refer to the core protocol.

10 REFERENCES

Bourla and Zamarin 2016
Bourla AB, Zamarin D. Immunotherapy: new strategies for the treatment of gynecologic malignancies. Oncology (Williston Park). 2016;30(1):59-66, 69.

Galluzzi et al 2012
Galluzzi L, Senovilla L, Zitvogel L, Kroemer G. The secret ally: immunostimulation by anticancer drugs. Nat Rev Drug Discov. 2012;11(3):215-33.

Garassino et al 2017
Garassino M, Vansteenkiste J, Joo-Hang Kim, Hervé Léna, Mazières J, Powderly J et al. PL04a.03: durvalumab in ≥3rd-line locally advanced or metastatic, EGFR/ALK Wild-Type NSCLC: results from the Phase 2 ATLANTIC Study. J Thor Onc. 2017;12:S10–S11.

Goss et al 2010
Goss GD, Arnold A, Shepherd FA, Dediu M, Ciuleanu TE, Fenton D et al. Randomized, double-blind trial of carboplatin and paclitaxel with either daily oral cediranib or placebo in advanced non-small-cell lung cancer: NCIC clinical trials group BR24 study. J Clin Oncol. 2010;28(1):49-55.

Hamanishi et al 2015
Hamanishi J, Mandai M, Ikeda T, Minami M, Kawaguchi A, Murayama T et al. Safety and antitumor activity of anti-PD-1 antibody, nivolumab, in patients with platinum-resistant ovarian cancer. J Clin Oncol. 2015;33:4015–22.

Kandalaft et al 2011
Kandalaft LE, Motz GT, Busch J, Coukos G. Angiogenesis and the tumor vasculature as antitumor immune modulators: the role of vascular endothelial growth factor and endothelin. Curr Top Microbiol Immunol. 2011;344:129-48.

Laurie et al 2014
Laurie SA, Solomon BJ, Seymour L, Ellis PM, Goss GD, Shepherd FA et al. Randomised, double-blind trial of carboplatin and paclitaxel with daily oral cediranib or placebo in patients with advanced non-small cell lung cancer: NCIC Clinical Trials Group study BR29. Eur J Cancer. 2014;50(4):706-12.

Lee et al 2016
Lee J, Cody P, Cimino-Mathews A, Zimmer A, Lipkowitz S, Annunziata CM et al. Phase I study of the PD-L1 inhibitor, durvalumab (MEDI4736) in combination with a PARP inhibitor, olaparib or a VEGFR inhibitor, cediranib in women's cancers. J Clin Oncol. 2016:34(15)(suppl);abstr 3015.

Lee et al 2017
Lee JM, Cimino-Mathews A, Peer CJ, Zimmer A, Lipkowitz S, Annunziata CM et al. Safety and clinical activity of the programmed death-ligand 1 inhibitor durvalumab in combination with poly (ADP-ribose) polymerase inhibitor olaparib or vascular endothelial growth factor receptor 1-3 inhibitor cediranib in women's cancers: A dose-escalation, phase I study. J Clin Oncol. 2017;35(19):2193-202.

Matulonis et al 2019
Matulonis UA, Shapira-Frommer R, Santin AD, Lisyanskaya AS, Pignata S, Vergote I et al. Antitumor activity and safety of pembrolizumab in patients with advanced recurrent ovarian cancer: results from the Phase 2 KEYNOTE-100 Study. Ann Oncol. 2019;30(7):1080-7.

Motz et al 2014
Motz GT, Santoro SP, Wang LP, Garrabrant T, Lastra RR, Hagemann IS et al. Tumor endothelium FasL establishes a selective immune barrier promoting tolerance in tumors. Nat Med. 2014;20(6):607-15.

Narwal et al 2013
Narwal R, Roskos LK, Robbie GJ. Population pharmacokinetics of sifalimumab, an investigational anti-interferon alpha monoclonal antibody, in systemic lupus erythematosus. Clin Pharmacokinet. 2013;52(11):1017–27.

Ng et al 2006
Ng CM, Lum BL, Gimenez V, Kelsey S, Allison D. Rationale for fixed dosing of pertuzumab in cancer patients based on population pharmacokinetic analysis. Pharm Res 2006;23(6):1275–84.

Oelkrug and Ramage 2014
Oelkrug C, Ramage JM. Enhancement of T cell recruitment and infiltration into tumours. Clin Exp Immunol. 2014;178(1):1-8.

Petit and Basu 2013
Petit RG, Basu P. ADXS11-001 immunotherapy targeting HPV-E7: updated survival and safety data from a phase 2 study in Indian women with recurrent/refractory cervical cancer. J Immunother Cancer. 2013;1(Suppl 1):P231.

Socinski et al 2018
Socinski MA, Jotte RM, Cappuzzo F, Orlandi F, Stroyakovskiy D, Nogami N et al; IMpower150 study group. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. N Engl J Med. 2018;378(24):2288-2301.

Wang et al 2009
Wang DD, Zhang S, Zhao H, Men AY, Parivar K. Fixed dosing versus body size-based dosing of monoclonal antibodies in adult clinical trials. J Clin Pharmacol. 2009;49(9):1012–24.

Zhang et al 2012
Zhang S, Shi R, Li C, Parivar K, Wang DD. Fixed dosing versus body size-based dosing of therapeutic peptides and proteins in adults. J Clin Pharmacol. 2012;52(1):18–28.

Clinical Study Protocol

Drug Substance	Umbrella study
Study Code	D6185C00001 (HUDSON)
Version	14.0
Date	09 October 2024

Appendix P

Module 8: AZD6738 (ceralasertib) monotherapy

An Open-Label, Multi-Drug, Biomarker-Directed, Multi-Centre Phase II Umbrella Study in Patients with Non-Small Cell Lung Cancer, who Progressed on an Anti-PD-1/PD-L1 Containing Therapy (HUDSON)

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

Regulatory Agency Identification Numbers:

EudraCT number: 2017-002208-28

EU CT number: 2023-509004-15-00

IND number: 138050

VERSION HISTORY

Version 14.0, 09 October 2024

Key amendments and rationale for changes:

Section 2.2.1.3, AZD6738 monotherapy safety data: CCI [redacted] when AZD6738 is used as monotherapy and in combination with durvalumab.

Section 6.5.2, drug-drug interaction between AZD6738 and other drugs; Section 11, AZD6738 drug-drug interactions: Updated to describe AZD6738 as an inducer of CYP CCI CYP CCI and CYP CCI and a weak inhibitor of CYP CCI and CYP CCI

Section 8.4.1, reporting of serious adverse events: addition of text relating to the reporting of MDS and/or AML during follow-up.

Section 8.4.5, management of study drug-related toxicities:

- Guidance was added for patients who experience suspected MDS/AML.
- New sub-section was added to describe actions to be taken if a patient displays suspected indications of MDS and/or AML.

Table 7, drugs known to be inhibitors and inducers of CYP CC: Ceralasertib was added as a potent CYP CC inducer.

Minor text clarifications were also made.

Version 13.0, 14 December 2023

Key amendments and rationale for changes:

Front page: EU CT number has been added in line with the core CSP.

Section 6.1.1, study drugs: Text regarding 'Packaging and Labelling' updated to remove the information that labels will fulfil GMP Annex 13 requirements for labelling, as this Annex has been replaced.

Version 12.0, 01 March 2023
Key amendments and rationale for changes: **Section 6.2, preparation/handling/storage/accountability:** Added a reference to the Pharmacy Manual.

Version 11.0, 16 August 2022
Key amendments and rationale for changes: **Table 1, schedule of activities:** • Removal of CCI sample collection on Day 15 (Cycles 1 and 2), text related to collection days for subsequent cycles deleted and footnote added to clarify timing of sample collection. This change is made to align with other AstraZeneca projects. • Addition of footnote to clarify an on-treatment biopsy is not required if a fresh tumour sample is not collected at pre-screening. Analysis requires a baseline result for comparison (ie, from the pre-screening sample).

Version 10.0, 12 April 2022
Key amendments and rationale for changes: **From implementation of protocol v10.0, patient recruitment to Module 8 is closed:** Text added to Section 2, introduction and Section 4.1, overall design. **Table 1, schedule of activities:** • Addition of footnote to clarify the activities for patients continuing on study treatment after the data cut-off for the module clinical study report. • Clarified that the safety follow-up visit can be conducted by telephone as there are no study-specific blood samples at this time point. • Blood sample for PBMCs for flow cytometry label clarified. • Additional blood sample at Cycle 2 Day 15 visit included for the following assessments: circulating soluble factors, gene expression, immunophenotyping, and TCR immuno-sequencing. To monitor pharmacodynamic activity of AZD6738. • Additional blood sample at study drug discontinuation visit included for the following assessments: Immunophenotyping and TCR immuno-sequencing. To evaluate immune phenotype status at discontinuation of study drug.

Figure 1, study design: Addition of footnote to clarify survival follow-up of screen failures is no longer required from implementation of protocol v10.0.

Section 2.2.1.2, AZD6738 clinical programme; Section 2.2.1.3; AZD6738 monotherapy safety data; new Section 2.2.1.5, emerging data from Module 8 of HUDSON: Text updated to align with AZD6738 IB Edition 10 and reference to the current IB added.

Section 4.3, justification for AZD6738 dose: Number of patients dosed in Module 3 of Study D5330C00004 was updated and sentence added for the recommended Phase II dose from Module 3 in this study.

Table 4, supportive medication:

- Text added to provide guidance for the use and timing of authorised and approved COVID-19 vaccines, to align with the COVID-19 vaccination guidance letter (dated 24 February 2021) provided to sites.
- Text added to clarify when AZD6738 treatment should be discontinued and restarted before and after a patient undergoes palliative radiation treatment to align with the Ceralasertib Project Specific Safety Requirements v14.

Section 6.5.2, drug-drug interaction between AZD6738 and other drugs; Section 11 AZD6738 drug-drug interactions: Text and associated tables updated per the Ceralasertib Project Specific Safety Requirements v14.

Table 6, dose interruption and stopping criteria: To align with the Ceralasertib Project Specific Safety Requirements v14, the table title and text for Grade 1-2 toxicities were updated.

Section 8.6, pharmacodynamics: Text updated to clarify pharmacodynamic parameters will be evaluated in the study and a cross reference to Section 8.6 of the core protocol added.

Version 9.0, 14 May 2021

Key amendments and rationale for changes:

Revisions to Module 8 are described in the version history of Version 8.1 and Version 9.0 of Module 8. Please refer to both sections of the version history for a complete summary of changes.

Additional safety assessments have been added based on reported adverse events of Grade ≥ 3 haematological toxicity including: anaemia, thrombocytopenia, neutropenia (including a Grade 3 febrile neutropenia in one patient) in 4 patients, out of a total of

8 patients, who received AZD6738 at the 240 mg BD dose (2 weeks on and 2 weeks off in a 4-week cycle) across 2 ongoing AZ sponsored studies, as of 15APR21 (PLANETTE [D5339C00001; n=3 of 4 patients]) and HUDSON [Module 8 and Module 9; n=1 of 4 patients]).

Further details are summarised in the Urgent Safety Measure notification (22APR2021) and Investigator letters (16APR21, and 14MAY21).

Schedule of Activities (Table 1):

- Anaemia and/or neutropenia have been added to the Grade ≥3 haematological toxicities that would necessitate additional safety visits and assessments.

Section 6.6 Dose modification:

- Section updated to add that patients who develop an event of ≥ Grade 3 of thrombocytopenia, anaemia, and/or neutropenia later than Cycle 2 in their treatment will need to have additional assessment on Day 8 (± 1 day window) until there is no evidence of ≥ Grade 3 thrombocytopenia, anaemia, and/or neutropenia for at least 2 cycles.

Version 8.1, 28 April 2021

Key amendments and rationale for changes:

Schedule of Activities (Table 1):

- Additional haematology and clinical chemistry monitoring visits have been added on Day 8 (± 1 day window) of Cycles 1 and 2 to monitor toxicity, with the possibility of including the additional haematology and clinical chemistry monitoring visits in subsequent cycles later in treatment, as clinically indicated.

  This measure is based on investigator-reported adverse events of Grade ≥ 3 haematological toxicity including: anaemia, thrombocytopenia, neutropenia (including febrile neutropenia in one patient) in 4 patients who received AZD6738 in the HUDSON study, and in 4 patients who received AZD6738 in the AstraZeneca-sponsored PLANETTE study (Study D5339C00001) as of the data-cut-off date 14APR2021.

  While anaemia and thrombocytopenia are considered expected events for AZD6738 monotherapy (per the reference safety information (Section 5.6 of the AZD6738 Investigator's Brochure [Edition 9.0]), as these events occurred early after study/cohort initiation, AstraZeneca has taken the decision to introduce additional safety monitoring visits as a precautionary measure.

Section 2.2.1.4 (Emerging data from Module 3 of HUDSON and rationale for assessing AZD6738 monotherapy in Module 8):

- Emerging data up to the data-cut-off-date of 26JAN21 added from Module 3 of HUDSON.

Version 8.0, 11 September 2020

Key amendments and rationale for changes:

Schedule of Activities (Table 1):

- Update to the table: Number of samples for CCI assessment reduced after Week 24 to once every 3 cycles rather than once every cycle. To reduce the sampling burden on patients.
- Change to allow physical examination at Day 15 of each cycle to be conducted only if clinically indicated.
- Drug accountability removed from Cycle 1 Day 1 visit, as it is not applicable.
- Footnote d added to the table to specify that in case of drug discontinuation within the planned Day 1-14 dosing window (for any reason), resumption of treatment can only take place within the planned dosing window and not beyond.

Section 1.3.1 (Safety Run-in): Revised from a formal safety run-in to a safety review in which recruitment will continue while the review of safety data from the first 6 patients is ongoing. This is due to availability of additional safety information for the AZD6738 dose and schedule in a similar disease setting to this module, which indicates that the AZD6738 dose being used in Module 8 is well tolerated.

Section 6.2.1 (Study Drug Administration): Text added that in case of drug discontinuation of AZD6738 within the planned Day 1-14 dosing window (for any reason), resumption of treatment can only take place within the planned dosing window and not beyond.

Table 6: Updates to the dose interruption and stopping criteria based on emerging safety information.

Version 7.0, 21 May 2020

Initial creation

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

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1. PROTOCOL SUMMARY

1.1 Schedule of Activities (SoA)

The Schedule of Activities (SoA) for the on-treatment period for Module 8 is shown in Table 1 below. For the SoA for the pre-screening and main screening visits, please refer to the core protocol.

This module will conduct a safety review comprising approximately 6 patients for 1 cycle. See Section 1.3.1 for further details.

Table 1 Schedule of Activities – Treatment intervention period (Module 8)

	C1 28 days Weeks 1-4			**C2** 28 days Weeks 5-8			**C3 - etc** **All cycles 28 days**			**Study drug disc.** (28 days after study drug disc.)	**Safety follow-up** (90 days after study drug disc.)[h]	**Survival follow up**	**Notes**
Week	**1**	**2**	**3**	**5**	**6**	**7**	**9, 10, 13, 17 etc**						
Day of cycle	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8[e]**	**15[b]**				
Window (days)	**0[a]**	**±1**	**+2**	**±2**	**±1**	**+2**	**±2**	**±1**	**+2**	**±7**	**±7**	**±7**	
Study procedures[i]													
Physical examination	X		X (if clinically indicated)	X		X (if clinically indicated)	X		X (if clinically indicated)	X			Section 8.2.2 (core protocol)
Vital signs[c]	X	X	X	X	X	X	X	X	X	X			Section 8.2.3 (core protocol)
ECG	X			X			X						Section 8.2.4 (core protocol)
Concomitant medications	X	X	X	X	X	X	X	X	X	X			Section 6.5
Laboratory assessments[i]													
Clinical chemistry	X	X[d]	X	X	X[d]	X	X	X	X	X			

	C1 28 days Weeks 1-4			**C2** 28 days Weeks 5-8			**C3 - etc** **All cycles 28 days**			**Study drug disc.** (28 days after study drug disc.)	**Safety follow-up** (90 days after study drug disc.)[h]	**Survival follow up**	**Notes**
Week	**1**	**2**	**3**	**5**	**6**	**7**	**9, 10, 13, 17 etc**						
Day of cycle	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8[e]**	**15[b]**				
Window (days)	**0[a]**	**±1**	**+2**	**±2**	**±1**	**+2**	**±2**	**±1**	**+2**	**±7**	**±7**	**±7**	
Haematology	X	X[d]	X	X	X[d]	X	X	X	X	X			Section 8.2.1 (core protocol). If screening laboratory assessments are performed within 3 days prior to Day 1 they do not need to be repeated
APTT and INR	X	As clinically indicated											
TSH, free T_3 and free T_4	X		X	X		X	X		X	X			Section 8.2.1 (core protocol)
Urinalysis	X	As clinically indicated											Section 8.2.1 (core protocol)
Pregnancy test	X			X			X			X			Section 8.2.1.2 (core protocol)

	C1 28 days Weeks 1-4			**C2** 28 days Weeks 5-8			**C3 - etc** **All cycles 28 days**			**Study drug disc.** (28 days after study drug disc.)	**Safety follow-up** (90 days after study drug disc.)[h]	**Survival follow up**	**Notes**
Week	**1**	**2**	**3**	**5**	**6**	**7**	**9, 10, 13, 17 etc**						
Day of cycle	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8[e]**	**15[b]**				
Window (days)	**0[a]**	**±1**	**+2**	**±2**	**±1**	**+2**	**±2**	**±1**	**+2**	**±7**	**±7**	**±7**	
AE/SAE	X	X	X	X	X	X	X	X	X	X	X		Section 8.3 (core protocol)
Study drug administration[i]													
AZD6738[f]	X Days 1-14			X Days 1-14			X Days 1-14						Section 6.1
Drug accountability			X	X		X	X			X			Section 6.2.3
Other administration													
Blood for CCI assessments[j]	X			X			X			X			Section 8.8 (core protocol)
Circulating soluble factors	X		X	X		X	X (Cycle 4 only)			X			Section 8.8 (core protocol)
Whole blood for gene expression (PAXgene RNA tubes)	X		X	X		X	X (Cycle 4 only)			X			Section 8.8 (core protocol)

	C1 28 days Weeks 1-4			**C2** 28 days Weeks 5-8			**C3 - etc** **All cycles 28 days**			**Study drug disc.** (28 days after study drug disc.)	**Safety follow-up** (90 days after study drug disc.)[h]	**Survival follow up**	**Notes**
Week	**1**	**2**	**3**	**5**	**6**	**7**	**9, 10, 13, 17 etc**						
Day of cycle	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8[e]**	**15[b]**				
Window (days)	**0[a]**	**±1**	**+2**	**±2**	**±1**	**+2**	**±2**	**±1**	**+2**	**±7**	**±7**	**±7**	
PBMCs for flow cytometry (immunophenotyping activation by / PD-1 CD8+)	X		X	X		X	X (Cycle 4 only)			X			Section 8.8 (core protocol)
TCR immuno-sequencing	X		X	X		X	X (Cycle 4 only)			X			Section 8.8 (core protocol)
Tumour evaluation (CT or MRI, RECIST 1.1)				Every 6 weeks ±1 week for the first 24 weeks relative to the start of therapy (Cycle 1 Day 1), then every 8 weeks ±1 week thereafter, until objective disease progression as defined by RECIST 1.1 and confirmed with a subsequent scan (in the absence of clinically significant deterioration)									Section 8.1 (core protocol)
Biopsy on treatment (mandatory)[k]						X							Section 8.8 (core protocol). This should align with the first RECIST assessment
Biopsy on disease progression										X			Section 8.8 (core protocol)

	C1 28 days Weeks 1-4			**C2** 28 days Weeks 5-8			**C3 - etc** **All cycles 28 days**			**Study drug disc.** (28 days after study drug disc.)	**Safety follow-up** (90 days after study drug disc.)[h]	**Survival follow up**	**Notes**
Week	**1**	**2**	**3**	**5**	**6**	**7**	**9, 10, 13, 17 etc**						
Day of cycle	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8[e]**	**15[b]**				
Window (days)	**0[a]**	**±1**	**+2**	**±2**	**±1**	**+2**	**±2**	**±1**	**+2**	**±7**	**±7**	**±7**	
Subsequent cancer therapy											X	X	Section 8.1.3.1 (core protocol). To be done every 3 months
Survival status												X[g]	Section 8.1.3.1 (core protocol). To be done every 3 months

[a] Every effort should be made to minimise the time between allocation and starting treatment. Note, if main screening assessments have been performed within 3 days prior to C1D1, then assessments do not need to be performed on C1D1 pre-dose.

[b] If toxicity of ≥ Grade 3 is observed during Cycles 1 and/or 2, patients should return for additional visits on Day 15 of subsequent cycles to ensure appropriate safety follow up, per investigator judgement, of the events observed in previous cycles.

[c] If clinically indicated, blood pressure to be measured in the supine and standing positions after at least 10 minutes' rest.

[d] Haematology and clinical chemistry assessments will take place on Day 8 (± 1 day window) of Cycles 1 and 2. If any toxicity is detected during these additional safety assessments, the patient will be managed as per the protocol, and as clinically indicated. In the event that a patient has an event of thrombocytopenia, anaemia and/or neutropenia that is ≥ Grade 3 during the first 2 cycles, this additional safety assessment will be included in subsequent cycles until there is no evidence of ≥ Grade 3 thrombocytopenia, anaemia and/or neutropenia for at least 2 cycles.

[e] Patients who develop an event ≥ Grade 3 of thrombocytopenia, anaemia and/or neutropenia later in their treatment will also need to have this additional assessment until there is no evidence of ≥ Grade 3 thrombocytopenia, anaemia and/or neutropenia for at least 2 cycles.

[f] Patients must receive AZD6738 for 14 days within a 28-day cycle. A cycle must not be < 28 days. AZD6738 must not be given on any other days of the cycle, and dosing days must stay relative to Day 1 of each cycle. In case of drug discontinuation within the planned Day 1 to 14 dosing window (for any reason), resumption of treatment can only take place within the planned dosing window and not beyond, even if this means the subject receives less than the specified 14 days AZD6738 dosing in the particular cycle.

[g] Ad hoc collection of survival status may be requested for overall survival analyses.

[h] If appropriate, the safety follow-up can be a telephone contact with the patient with the information recorded in the eCRF.

[i] Following the final data cut-off for the module CSR (see Section 9.4.2 of the core protocol), any patients on study treatment may continue on treatment and should be assessed for safety according to standard local clinical practice. Study drug administration, SAE reporting and related safety assessment data should be recorded in the eCRF until 90 days after study drug discontinuation, when the patient will end participation in the study. The other assessments for the study will no longer be performed and those data will no longer be collected; the tumour evaluations will be performed as per standard of care. The survival follow-up will no longer be conducted.

[j] Whole blood to be taken every cycle for the first 3 cycles and at every radiographic assessment visit (every 6 weeks [± 1 week] for the first 24 weeks relative to the start of therapy (C1D1), then every 8 weeks [±1 week]) in all patients (at pre-dose on AZD6738 dosing day) until disease progression (or study treatment discontinuation).

[k] On-treatment biopsy is not required if a fresh tumour sample is not collected at pre-screening.

AE adverse event; APTT activated partial thromboplastin time; C cycle; CD8+ cytotoxic T-cell; CSR clinical study report; CT computed tomography; CC[redacted] D day; ECG electrocardiogram; eCRF electronic Case Report Form; INR international normalised ratio; RECIST 1.1 Response Evaluation Criteria in Solid Tumours 1.1; MRI magnetic resonance imaging; PBMC peripheral blood mononuclear cell; PD-1 programmed cell death-1; SAE serious adverse event; TCR T-cell receptor repertoire; TSH thyroid-stimulating hormone; T_3 triiodothyronine; T_4 thyroxine.

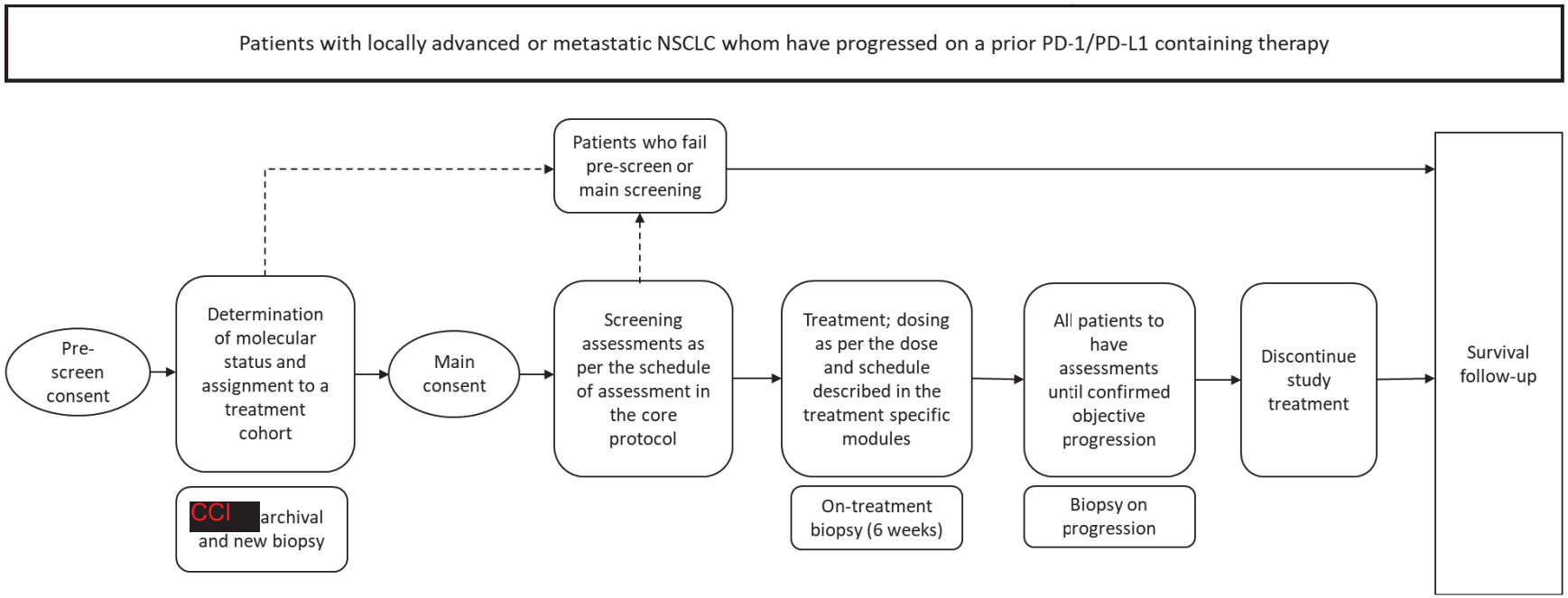
1.2 Synopsis

Please refer to Section 1.2 of the core protocol.

1.3 Schema

The general study design is summarised in Figure 1.

Figure 1 Study design



Note, as of implementation of protocol v10.0, survival follow-up of screen failures is no longer applicable.
CCI NSCLC non-small cell lung cancer; PD-1 programmed cell death-1; PD-L1 programmed cell death-ligand 1.

1.3.1 Safety review

A comprehensive review of all safety data will be conducted in approximately the first 6 patients; these patients will be followed for 1 cycle to ensure the treatment schedule is safe and tolerable. The study procedures and safety assessments undertaken for the first cycle will be as per the SoA (Table 1). Recruitment will continue whilst the safety review is performed. The safety assessment will be undertaken by a Safety Review Committee (SRC). The role and responsibilities of SRC members, as well as the purpose and timing of the SRC meetings are described in the SRC Charter (core protocol Appendix A).

2. INTRODUCTION

Study D6185C00001 (HUDSON) is a Phase II, open-label, multi-centre umbrella study in patients who have received an anti-programmed cell death-1 (PD-1)/anti-programmed cell death-ligand 1 (PD-L1) containing therapy and a platinum-doublet regimen for locally advanced or metastatic non-small cell lung cancer (NSCLC) either separately or in combination. The patient must have had disease progression on a prior line of anti-PD-1/PD-L1 therapy. The modular design allows the evaluation of the efficacy, safety, and tolerability of multiple study drugs. This module to the core study protocol describes Module 8, which will investigate the efficacy, safety, and tolerability of AZD6738 monotherapy. As of implementation of protocol version 10.0, Module 8 is closed to patient recruitment.

2.1 Study rationale

As described in Section 2.2 of the core protocol, immune checkpoint inhibitors targeting the PD-1/PD-L1 pathway have shown significant activity in the first- and second-line treatment settings in patients with NSCLC. However, it is becoming evident that there is a new and significant patient population emerging that does not respond to anti-PD-1/PD-L1 containing therapy (primary resistance) or progresses during anti-PD-1/PD-L1 containing therapy (acquired resistance). There is currently no established therapy for patients who have developed resistance to PD-1/PD-L1 and platinum-doublet therapies, and novel treatments for these patients are urgently needed.

The aim of this umbrella study (D6185C00001) is to investigate multiple study drugs for the treatment of NSCLC in molecularly matched and non-matched patient populations after failure of immune checkpoint inhibitors, to identify patient populations who may respond favourably to novel anti-tumour therapies.

2.2 Background

AZD6738 (Note: per IB, AZD6738 is also known as ceralasertib) is currently in clinical development as an anti-cancer therapy in a variety of malignancies.

Module 8 will investigate AZD6738 monotherapy in patients whose tumours are deficient in ATM. Brief background on AZD6738, including its mechanisms of action, is provided below. For detailed descriptions of the chemistry, pharmacology, efficacy, and safety of AZD6738, refer to the Investigator's Brochure.

The study will recruit biomarker-matched patients (see Section 4.1); the biomarker is the enzyme ATM (see Section 2.2.1).

2.2.1 AZD6738

2.2.1.1 Overview of AZD6738

AZD6738 is a potent, selective inhibitor of ataxia telangiectasia and Rad3-related protein (ATR), with good selectivity against other phosphatidylinositol 3-kinase-related kinase (PIKK) family members. This compound is being developed as an oral anti-tumour agent in patients with disease that is dependent upon ATR function for DNA repair; an example being tumours that are deficient of the serine/threonine specific protein kinase, ataxia telangiectasia mutated (ATM).

ATR is a serine/threonine protein kinase and member of the PIKK family. During normal DNA replication, ATR is activated by persistent single-strand DNA breaks (SSBs) that occur if a replication fork is stalled in S-phase during DNA synthesis. Activation of ATR triggers a signal cascade leading to cell cycle arrest in S-phase whilst the DNA is repaired and the stalled replication fork resolved. Without repair, SSBs can progress to double-strand DNA breaks (DSBs), the most genotoxic form of DNA damage due to the consequences DSBs have for accurate chromosome segregation during cell division (O'Connor 2015). ATR is also recruited to single-strand DNA coated with Replication Protein A following single strand DNA damage or the resection of DSBs.

AZD6738 is an inhibitor of ATR that blocks this activity, causing stalled replication forks to collapse leading to DSBs and a dependence on ATM, a key enzyme co-ordinating the cellular response to DSBs (Weber and Ryan 2015). If the level of DNA damage exceeds the capacity to repair, nuclear fragmentation and entry into programmed cell death (apoptosis) occur (Cimprich and Cortez 2008).

ATM is a closely related kinase that is recruited to DSBs and, like ATR, has both checkpoint and repair functions. In normal cells, there is a significant interplay between ATR and ATM as stalled replication forks can be converted into DSBs through further DNA damage and the resection of DSBs generates single-stranded DNA (Stewart et al 2015; Toledo et al 2011). Sporadic ATM deficiency is reported in many tumour types, and ATM deficiency is expected to sensitise tumour cells to ATR inhibition through their complementary roles in DNA damage repair. Patients with ATM-deficient malignancies can be clinically identified and, in

most cases, are known to have a poor prognosis with current therapies. ATM expression is commonly lost/reduced in NSCLC (Villaruz et al 2016).

Preclinically AZD6738 has demonstrated antitumour activity in gastric cancer cells. In SNU-601 cells with dysfunctional ATM, AZD6738 treatment led to an accumulation of DNA damage due to dysfunctional RAD51 foci formation, S-phase arrest, and caspase 3-dependent apoptosis, whereas SNU-484 cells with functional ATM were not sensitive to AZD6738. In addition, in an in vivo tumour xenograft mouse model, AZD6738 significantly suppressed tumour growth and increased apoptosis. These findings suggest synthetic lethality between ATR inhibition and ATM deficiency in gastric cancer cells (Min et al 2017).

2.2.1.2 AZD6738 clinical programme

Currently, for the ATR programme, there are a number of ongoing AstraZeneca sponsored clinical studies with AZD6738 in addition to HUDSON, where combinations of AZD6738 with carboplatin, olaparib or durvalumab are being explored.

There are 3 other AstraZeneca sponsored studies incorporating AZD6738:

D419QC00002 study (BALTIC, NCT02937818), using AZD6738 and olaparib combination in patients with platinum refractory extensive-stage small-cell lung cancer, has completed with 21 patients dosed. D5336C00001 (VIOLETTE study, NCT03330847) using the AZD6738 and olaparib combination in patients with triple negative breast cancer with BRCA mutation (stratum A), HRR mutation (stratum B) and non-HRR mutation (stratum C), was closed based on primary analysis CCI Based on primary analysis in stratum A of the D5336C00001 study, D6018C00004 (DUETTE, NCT04239014), using the combination of AZD6738 and olaparib as second maintenance treatment in patients with platinum-sensitive relapsed epithelial ovarian cancer, who have previously received PARP inhibitor maintenance treatment, was terminated (C patients were randomised to treatment).

A previous Phase I study (D5330C00001; NCT01955668) to assess multiple ascending doses of AZD6738 in patients with prospectively identified 11q-deleted relapsed/refractory chronic lymphocytic leukaemia (CLL), prolymphocytic leukaemia or B cell lymphomas was stopped after one patient was treated, due to difficulties in recruitment. An AstraZeneca sponsored study (D5330C00008, NCT03328273) is testing AZD6738 combination with acalabrutinib in patients with relapsed/refractory CLL; the monotherapy part of the study has been stopped due to difficulties in recruiting the required patient population.

In addition, there are Externally Sponsored Research (ESR) studies ongoing where AZD6738 is being investigated as a single agent or in combination with radiotherapy (PATRIOT study [D5330C00002; NCT02223923]; recruitment complete), in combination with paclitaxel or durvalumab (Pre-VIKTORY study [D5330C00006; NCT02630199] in patients with advanced solid tumours and enriched with metastatic melanoma, and VIKTORY study [D6183C00003;

NCT02299648] in patients with metastatic melanoma and gastric cancer; recruitment complete in both studies), or in combination with olaparib in ovarian carcinoma (CAPRI study [D5334C00001; NCT03462342]) and in patients with solid tumours harbouring mutations in homology-directed repair genes (OLAPCO [D0810C00090; NCT02576444]; recruitment complete), in patients with relapsed small cell lung cancer (SUKES-N2 [D5334C00003; NCT03428607]; recruitment complete), in triple negative breast cancer (PlasmaMATCH Cohort E [D6184C00001; NCT03182634]; recruitment complete), and in BAF250a (ARID1A)-deficient or BAF250a-expressing advanced solid cancers (D5330C00012; NCT03682289).

AZD6738 monotherapy has been administered in 4 studies:

- Study D5330C00004 (NCT02264678; solid malignancies) - 80 mg twice daily or 160 mg once daily 21 days on and 7 days off in a 28-day cycle
- Study D5330C00008 (NCT03328273; haematological malignancies) - 160 mg twice daily every day, and 160 mg twice daily from Days 1 to 14 of a 28-day cycle
- Study D5330C00007 (NCT03022409; HNSCC) - 160 mg twice continuously for minimum of 10 days and maximum of 21 days
- Study D5339C00001 (PLANETTE; metastatic castration-resistant prostate cancer [mCRPC] and advanced solid tumours) Module 1 – 160 mg twice daily for 14 days in a 28-day cycle (dose reduced from initial starting dose of 240 mg twice daily for 14 days in a 28-day cycle)

See the current Investigator's Brochure for further information.

2.2.1.3 AZD6738 monotherapy safety data

Safety data are available for AZD6738 monotherapy from Study D5330C00004 (solid malignancy), Study D5330C00008 (haematological malignancies), Study D5330C00007 (solid tumours: HNSCC) and Study D5339C00001 (ATM deficient solid tumours), based on a data cut-off date of 13 June 2021.

Overall, the most common AEs (reported in > 20% of patients who received AZD6738) for patients in Study D5330C00004 were CCI [redacted]

The most common AEs for patients in Study D5330C00008 CCI [redacted]

The most common AEs for patients in Study D5330C00007 were CCI

The most common AEs for patients in Study D5339C00001 were platelet count decreased and fatigue (4/8 [50.0%] patients each), CCI patients; CCI Grade ≥ 3), CCI patients each), CCI patients each; all Grade ≥ 3).

The SAE reported in Study D5330C00004 was atrial fibrillation. The most common SAEs in Study D5330C00008 were CCI patients) CCI patients). The SAE reported in Study D5330C00007 was chest pain. The most common SAE reported in Study D5339C00001 was CCI patients). CCI patient in Study D5339C00001 had an AE with an outcome CCI, an SAE of CCI that was considered by the investigator as causally CCI to treatment with AZD6738. Serious adverse reactions considered expected for safety reporting for AZD6738, either as monotherapy or various combinations, CCI

Anaemia, thrombocytopenia, and neutropenia (including febrile neutropenia), CCI have been reported when AZD6738 is used as monotherapy and when used in combination with durvalumab.

The AEs reported for AZD6738 monotherapy are consistent with those reported for AZD6738 in combination with either carboplatin, olaparib or durvalumab, were predictable from non-clinical data and from what is known about the mechanism of action of AZD6738 and/or the underlying disease. The observed toxicities in the clinical setting have been manageable with current clinical practice. See the Investigator's Brochure for further information.

The non-clinical and emerging safety profile has not identified any risks that would preclude investigation of AZD6738 monotherapy in the advanced cancer setting. Based on the identified and potential risks associated with treatment, this protocol incorporates mandatory safety monitoring procedures and additional guidance documents to assist with early diagnosis and rapid management of potential drug-related symptoms.

2.2.1.4 Emerging data from Module 3 of HUDSON and rationale for assessing AZD6738 monotherapy in Module 8

In the current Phase II, open-label, multicentre umbrella study (D6185C00001; HUDSON) the combined effects of AZD6738 and durvalumab in overcoming immune-resistance in patients who failed PD-1/PD-L1 containing therapy are being investigated. The efficacy, safety, and tolerability of durvalumab administered in combination with AZD6738 has been investigated in both biomarker-matched (A.3.ATM) and biomarker non-matched (B.3.PRI and B.3.ACQ) patients (Module 3).

As of 26 January 2021, C patients have been dosed in Module 3 (C A.3.ATM, 20 B.3.PRI and C B.3.ACQ). As per the data cut-off date (26 January 2021), all 65 dosed patients were evaluable for response, with CCI patients still on study treatment. The ORR across Module 3 was CCI In the A.3.ATM biomarker-matched cohort, which remains open for recruitment, the ORR was CCI In C evaluable patients a CCI disease control rate was observed at C weeks across Module 3 (CCI in the A.3.ATM cohort [CCI evaluable]). Landmark 6, 9 and 12 months PFS and OS data are CCI across all cohorts (although the C months OS data CCI for the A.3.ATM cohort).

The safety profile of durvalumab and AZD6738 combination in HUDSON has been CCI with other ongoing studies. Of the C patients with safety data available on file, the most frequent (≥ 15%) AEs were reported as: CCI The most commonly reported SAE across the durvalumab/AZD6738 combination was pneumonia in CCI patients. The majority of SAEs reported were confounded by risk factors other than study therapy such as medical history, concurrent conditions and concomitant medications. Overall, CCI patients discontinued treatment with AZD6738 due to AEs, and CCI of these patients also discontinued durvalumab. The overall safety was CCI At the time of preparation of protocol version 11.0, Module 3 is being expanded and is actively recruiting; therefore, data will be subject to change. For the most up-to-date information, please see the AZD6738 IB.

Observations made on samples taken at Cycle 0 Day 1 and Cycle 1 Day 1, representing the AZD6738 monotherapy treatment interval in Module 3 show evidence of CCI Specifically, AZD6738 monotherapy showed statistically significant CCI HUDSON data also included significant changes in CCI potentially linked with tumour promotion. These HUDSON data provide CCI of similar data from the AZD6738 Study D5330C00004. Taken together, these clinical datasets provide compelling CCI. These data confirm CCI within this post-anti-PD(L)-1 population.

Based on emerging clinical, safety and translational data, findings would suggest exploring AZD6738 monotherapy as a treatment option to overcome immune resistance in patients who have failed prior PD-1/PDL1 containing therapy.

2.2.1.5 Emerging data from Module 8 of HUDSON

As of the cut-off date of 13 June 2021, C patients have been dosed with AZD6738 (CCI for a maximum of 2 weeks per C -day cycle) in Module 8 of Study D6185C00001. The most common AEs were CCI An SAE of CCI patient), which was considered CCI to AZD6738 treatment. CC AEs led to death.

2.3 Benefit/risk assessment

As described in Section 2.3 of the core protocol, patients recruited to this study are not expected to have other treatment options apart from monotherapy chemotherapy, such as docetaxel. The survival outcome and toxicity profile of chemotherapy in this setting mean that other active therapies are highly desirable and present a potential advantage for patients.

The study design aims to identify patient populations who may respond favourably to novel anti-tumour therapies. Based upon the available non-clinical and clinical safety data, the limited survival benefit provided by the currently available treatment options to patients, and the limited life expectancy due to malignant disease, the investigation of the potential therapeutic efficacy of AZD6738 monotherapy in patients with advanced or metastatic NSCLC is acceptable, and the overall benefit/risk assessment supports the proposed study design.

3. OBJECTIVES AND ENDPOINTS

Please refer to the core protocol.

4. STUDY DESIGN

4.1 Overall design

This is an open-label, multi-centre, umbrella study in patients who have received an anti-PD-1/PD-L1 containing therapy and a platinum-doublet regimen for locally advanced or metastatic NSCLC either separately or in combination. The patient must have had disease progression on a prior line of anti-PD-1/PD-L1 therapy. For an overview of the study design see Figure 1; further details on the overall design are provided in Section 4 of the core protocol. For details on the study treatments given in Module 8, see Section 6.1.

Module 8 will evaluate the efficacy, safety, and tolerability of AZD6738 monotherapy (given orally) in biomarker-matched patients, as follows:

- **Cohort A.8.ATM** will investigate the efficacy, safety, and tolerability of AZD6738 monotherapy (given orally) in patients who are ATM-deficient (as determined using

immunohistochemistry [IHC]), or with detectable aberrations in the *ATM* gene (via next generation sequencing [NGS]).

As of implementation of protocol v10.0, patient recruitment to Module 8 is closed (refer to Section 4.1 of the core protocol for details).

A study flow diagram is provided in the core protocol (Figure 4).

4.2 Scientific rationale for study design

The study aims to identify patient populations who may respond favourably to novel anti-tumour therapies, and the modular design allows evaluation of the efficacy, safety, and tolerability of multiple study drugs. The study requires an open-label design owing to the different schedules and routes of administration of the study drugs.

Module 8 will include a biomarker-matched cohort A.8.ATM (ATM-deficient). The scientific background for inclusion of biomarker-matched cohort is as follows.

In tumour cells with ATM deficiency, the capacity for DSB repair is reduced so that treatment with AZD6738 leads to DSB accumulation and selective tumour cell death through apoptosis (Vendetti et al 2015). The death of ATM-deficient tumour cells is expected to release tumour antigens and change the tumour microenvironment to promote antigen presentation, priming the immune response (Galluzzi et al 2012).

Non-clinical models have suggested that ATM-deficient cell lines are sensitised to DNA damaging agents, including platinum chemotherapy and ATR inhibitors (Reaper et al 2011) (see Section 2.2.1.1).

Clinical studies of AZD6738 or other ATR inhibitors have shown encouraging efficacy in patients with ATM-deficient tumours:

- In Bayer's first-in-human study of the oral ATR inhibitor BAY 1895344 in patients with advanced solid tumours (NCT03188965), 22 patients with advanced metastatic solid tumours resistant or refractory to standard treatment, with and without DDR defects, were included across 6 cohorts. All 4 responders had ATM protein loss of expression and/or ATM mutation (De Bono et al 2019).
- In a Phase I study of olaparib and AZD6738 in relapsed, refractory cancer patients with HRR mutations, 24 previously pre-treated patients were enrolled. One of 5 patients with ATM mutations had a complete response, 2 patients had clinical benefit ongoing at more than 12 months (D5330C00004).
- The combination of olaparib and AZD6738 has demonstrated preliminary activity in patients with tumours harbouring ATM mutations and in PARPi-resistant BRCA1/2-mutated high grade serous ovarian carcinomas (D5330C00004).

- Signs of preliminary efficacy have been observed for durvalumab in combination with AZD6738 in Module 3 of HUDSON in patients with ATM mutation or protein expression loss previously treated with an immune checkpoint inhibitor (Section 2.2.1.4).
- AstraZeneca has recently initiated a study entitled "A Modular Phase 2a Multicentre Open-Label Study to Investigate DNA-damage Response Agents (or Combinations) in Patients With Advanced Cancer Whose Tumours Contain Molecular Alterations (PLANETTE)", which will include patients with advanced solid tumours excluding NSCLC and mCRPC with ATM loss alteration.

In Study D5330C00004, AZD6738 caused suppression of peripheral monocytes and proliferating T-cells during the dosing interval; both rebounding to levels ≥ baseline during the off-drug interval; the immunostimulatory cytokine IL-12 behaved similarly. These cyclical changes were observed across multiple treatment cycles. Granuclocyte-macrophage colony stimulating factor increased reciprocally to on-target decreases in monocytes. AZD6738 consistently increased pRAD50 in post-treatment tumour biopsies illustrating a mechanistic link between ATR inhibition and induction of the ATM pathway (Krebs et al 2018).

Taken together, these data suggest that patients in an ATM-deficient biomarker-matched cohort are most likely to respond favourably to AZD6738 monotherapy treatment.

4.3 Justification for AZD6738 dose

The dose of AZD6738 as monotherapy for this module is 240 mg twice daily from Day 1 to Day 14 of every 28-day cycle. This dose has been used as monotherapy and in combination with durvalumab 1500 mg administered on Day 1 of each 28-day cycle in Module 3 of Study D5330C00004 (NCT02264678) where C patients with NSCLC and SCHNN have been treated. AZD6738 240 mg twice daily was given as monotherapy in Cycle 0 for 14 days (Days 1 to 14) and then from Day 15 to Day 28 in each subsequent cycle in combination with durvalumab. In this study, AZD6738 240 mg bd 14 days combined with 1500 mg durvalumab Day 1 q28 was declared as the recommended Phase II dose.

AZD6738 240 mg twice daily from Day 15 to Day 28 of every 28-day cycle in combination with durvalumab 1500 mg administered on Day 1 of each 28-day cycle is also used in an ongoing ESR study in South Korea in patients with malignant melanoma (C patients) and metastatic gastric cancer (C patients) (as of 30 April 2020) (NCT02630199). This dose schedule of AZD6738 was not formally tested in PATRIOT (NCT02223923) in which 160 mg twice daily from Day C to Day C of every 28-day cycle, administered to C patients in the expansion cohort, was well-tolerated (data on file).

Preliminary safety data has shown that AZD6738 240 mg twice daily from Day C to Day C of every 28-day cycle is well tolerated as monotherapy as well as in combination with durvalumab (Study D5330C00004; data on file).

The dose level of 240 mg twice daily is predicted to maintain AZD6738 concentrations above the estimated concentration of an inhibitor where ATR catalytic activity is reduced by 90% (IC_{90}) threshold for 12 hours in 90% of patients (data on file). A sigmoid model links AZD6738 monotherapy exposure with the difference between CCI (PD modulation) and CCI (the main related CCI toxicity of AZD6738).

Based on the aforementioned data, the use of AZD6738 240 mg twice daily as monotherapy from Day 1 to Day 14 of every 28-day cycle in this module is justified.

AZD6738 240 mg twice daily as monotherapy from Day C to Day C will also be administrated in the planned study PLANETTE (study title "A Modular Phase 2a, Open-Label, Multicentre Study to Investigate DNA-Damage Response Agents [or Combinations] in Patients with Advanced Cancer whose Tumours contain Molecular Alterations") in which at least C patients with advanced solid tumours and C patients with mCRPC will initially be enrolled.

Furthermore, considering emerging PK data from ongoing studies, there is CCI

4.4 End of study definition

Please refer to the core protocol.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study in order to be assigned to a study cohort. Under no circumstances can there be exceptions to this rule. Patients who do not meet the entry requirements are screen failures; refer to Section 5.4 of the core protocol.

5.1 Inclusion criteria (Module 8-specific)

Patients are eligible to be included in the study only if all the following inclusion criteria apply. Please also refer to the Section 5.1 of the core protocol for the inclusion criteria applicable to all modules in the study. Additional inclusion criteria applicable to Module 8 only are described in this section.

P-1 Patients must fulfil all the core eligibility criteria.

P-2 Identification of molecular aberrations:

- Cohort A.8.ATM: patients who are ATM-deficient (as determined using IHC), or with detectable deleterious aberrations in the *ATM* gene (via NGS). Refer to the pathology and genomic testing manual for details of cohort composition, which will be informed by a combination of NGS and IHC data.

P-3 Washout of prior immunotherapy of ≥ 28 days.

5.2 Exclusion criteria (Module 8-specific)

Patients must not enter Module 8 of the study if any of the following exclusion criteria apply. Refer to Section 5.2 of the core protocol for the exclusion criteria applicable to all modules in the study. Additional exclusion criteria applicable to Module 8 only are described below:

Medical conditions

P-1 Diagnosis of ataxia telangiectasia.

P-2 Refractory nausea and vomiting, chronic gastrointestinal diseases or previous significant bowel resection, with clinically significant sequelae that would preclude adequate absorption of AZD6738.

P-3 Inadequate bone marrow reserve or organ function as demonstrated by any of the following laboratory values: absolute neutrophil count < 1.5 x 10^9/L; platelet count < 100 x 10^9/L; haemoglobin < 90 g/L.

P-4 Persisting (> 4 weeks) severe pancytopenia due to previous therapy rather than disease (absolute neutrophil count [ANC] < 1.5 x 10^9/L or platelets < 100 x 10^9/L).

P-5 Creatinine clearance < 45 mL/min calculated by Cockcroft-Gault equation (see Table 5 in the core protocol for the calculation).

P-6 Haematuria: +++ on microscopy or dipstick.

P-7 INR ≥ 1.5 or other evidence of impaired hepatic synthesis function.

P-8 Alkaline phosphatase >2.5 x upper limit of normal (ULN) (and liver disease unrelated to the tumour). Patients with elevated alkaline phosphatase (ALP) due to tumour related bone metastases or liver metastases will be eligible.

P-9 Patients with relative hypotension (< 100/60 mmHg) or clinically relevant orthostatic hypotension, including a fall in blood pressure of > 20 mmHg.

Prior/concomitant therapy

P-10 Concomitant use of known strong CYP3A inhibitors (eg, itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir). The required washout period prior to starting study intervention is 2 weeks.

P-11 Concomitant use of known strong CYP3A inducers (eg, phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort). The required washout period prior to starting study intervention is 5 weeks for enzalutamide or phenobarbital and 3 weeks for other agents.

P-12 Prior exposure to an ATR inhibitor.

Other

P-13 Inability to swallow the formulated product.

For procedures for withdrawal of incorrectly enrolled patients see Section 7.3 of the core protocol.

5.3 Lifestyle restrictions

Please refer to Section 5.3 of the core protocol for contraception requirements.

5.4 Screen failures

Please refer to the core protocol.

6. STUDY TREATMENTS

Study treatment is defined as any study drug(s) (including marketed product comparator and placebo) or medical device(s) intended to be administered to a study participant according to the study protocol. Study treatment in Module 8 refers to AZD6738.

6.1 Treatments administered

6.1.1 Study drugs

Table 2 Study drugs

	AZD6738
Dosage formulation:	Oral tablets in either 20, 80 or 100 mg
Route of administration:	Oral
Dosing instructions:	240 mg twice daily for 14 days on treatment in each 28-day cycle, between Days 1 and 14.
Packaging and labelling	Study drug will be provided in high-density polyethylene bottles with child-resistant closures. Labels will be prepared in accordance with GMP and local regulatory guidelines. The labels will fulfil GMP requirements for labelling. Label text will be translated into local language, as required. AZD6738 will be provided with either single-panel labels or multi-language booklet labels. Specific dosing instructions will not be included on the label; the site must complete the "Patient Dispensing Card" with the details of the dosing instructions at the time of dispensing. The Investigator's emergency contact details will not be on the label, but can be found in the informed consent and the 'Patient Dispensing Card'. For emergency purposes the patient must be in possession of the emergency contact details at all times.
Provider	AstraZeneca

GMP Good Manufacturing Practice

6.2 Preparation/handling/storage/accountability

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study drugs received and any discrepancies are reported and resolved before use of the study drug.

Only patients enrolled in the study may receive study drugs and only authorised site staff may supply or administer study drugs. All study drugs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorised site staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study drugs accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study drug are provided in the Pharmacy Manual.

6.2.1 Study drug administration

When AZD6738 is administered, patients must fast (water to drink only) for at least 2 hours prior to taking a dose, to at least 1 hour post-dose for all doses.

AZD6738 will be administered orally 240 mg twice daily, approximately 12 hours apart, starting on Day 1 until Day 14 of each treatment cycle, starting with Cycle 1. Patients must receive AZD6738 for 14 days within a 28-day cycle. A cycle must not be < 28 days. AZD6738 must not be given on any other days of the cycle, and dosing days must stay relative to Day 1 of each cycle. In case of drug interruption within the planned Day 1 to 14 dosing window (for any reason), resumption of treatment can only take place within the planned dosing window and not beyond, even if this means the subject receives less than the specified 14 days AZD6738 dosing in the particular cycle. Dosing after Cycle Day 14 is not permitted and the planned 14 days off treatment should not be reduced.

Patients are allowed to take the scheduled dose up to 2 hours after the scheduled dose time. If greater than 2 hours, the missed dose should not be taken and the patient should continue with next dose at the allotted time. If the patient wishes to bring forward the time of their scheduled dose, the dose can be taken up to a maximum of 2 hours prior to the scheduled time, ie, ± 2-hour window.

Patients should continue to receive study treatment until objective radiological disease progression as per Response Evaluation Criteria in Solid Tumours (RECIST 1.1), as long as, in the Investigator's opinion, they are benefiting from treatment and they do not meet any other discontinuation criteria. Disease progression should be confirmed by a subsequent scan (no earlier than 4 weeks later) in the absence of clinically significant deterioration as assessed by the Investigator. All patients who have objective progression of disease will enter follow-up.

6.2.2 Storage

All study drugs should be kept in a secure place under appropriate storage conditions.

The AZD6738 product label on the bottle specifies the appropriate storage.

The study drug must be kept in the original outer container and under conditions specified on the labels.

In the following cases, the centre staff should not use affected study drug and should immediately contact the AstraZeneca representative for further guidance:

- Temperature excursion upon receipt or during storage at the study
- Damaged kit upon receipt

- Damaged bottle

Damaged study drug should be documented according to the instructions provided by the AstraZeneca representative. Storage conditions stated in the Investigator's Brochure, or the study drug Handling Instructions document, may be superseded by the label storage.

6.2.3 Accountability

The study drugs provided for this study should only be used as directed in the study protocol.

The study site staff will account for all study drugs received at the centre, for unused study drugs, and for appropriate destruction (according to local procedures). Certificates of delivery, destruction, and/or return should be signed.

The administration of all medications (including study drug) and details of treatment with study drug should be recorded in the appropriate sections of the electronic Case Report Form (eCRF).

6.3 Measures to minimise bias: randomisation and blinding

This is an open-label study.

Recruitment to the biomarker-matched cohorts will be based upon a predefined schema (described in the Pathology and Genomic Testing Manual) for patient allocation which takes account of biomarker prevalence estimates and the platform of evidence for each study treatment.

If a patient withdraws from participation in the study, then his/her enrolment code cannot be reused. Withdrawn patients will not be replaced.

6.4 Treatment compliance

The administration of all study drugs should be recorded in the appropriate sections of the eCRF. Treatment compliance will be assured by reconciliation of site drug accountability logs. Patients will record their oral AZD6738 dosing on a diary which should be returned to the site at the next available visit. Sites should additionally record AZD6738 doses taken at site visits.

Patients will self-administer AZD6738. Patients should be given clear instructions on how and when to take their study treatment. Study site staff will make tablet counts at regular intervals during treatment when the bottles are returned per cycle. Compliance will be assessed by the tablet count and the information will be recorded in the appropriate section of the eCRF. After the tablet count has been performed, the remaining tablets will not be returned to the patient but will be retained by the investigative site until reconciliation is

completed by the study monitor. All patients must return their bottle(s) of AZD6738 at the appropriate scheduled visit, when a new bottle will be dispensed. Patients will be instructed to notify study site personnel of missed doses. Dates of missed or held doses will be recorded by the patient on their patient diary and by the site staff on the eCRF.

Patients must return all containers and any remaining tablets at their next scheduled treatment cycle and at the end of the study.

Any change from the dosing schedule, dose interruptions, dose reductions, dose discontinuations should be recorded in the eCRF.

The Study Drug Storage Manager is responsible for managing the study drug from receipt by the study site until the destruction or return of all unused study drug. The Investigator(s) is/are responsible for ensuring that the patient has returned all unused study drug.

Use of study treatment in doses in excess of that specified in the protocol is considered to be an overdose. Refer to Section 8.4.3 in the core protocol for procedures in case of overdose.

6.5 Concomitant therapy

Any medication or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the patient is receiving at the time of enrolment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Prohibited concomitant medications are described in Table 3. Please refer to Section 8.4.5 for guidance on management of study drug-related toxicities.

The use of concomitant medications must be recorded in the eCRF.

Table 3 Prohibited medications

Prohibited medication/class of drug	
Unless stated otherwise, these medications are prohibited from the time that patients enter the main screening period until the last dose of study treatment. The pre-screen may be done whilst on prior therapy.	
Any investigational anticancer therapy other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment
Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment. (Note: concurrent use of hormones for non-cancer-related conditions [eg, insulin for diabetes and hormone replacement therapy] is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable [eg, by local surgery or radiotherapy]). Patients may receive treatment with bisphosphonates or RANKL inhibitors for the treatment of bone metastases
Immunosuppressive medications, including, but not limited to: systemic corticosteroids at doses exceeding 10 mg/day of prednisone or its equivalent, methotrexate, azathioprine, and tumour necrosis factor-α blockers	Should not be given concomitantly, or used for premedication prior to the infusions. The following are allowed exceptions: • Use of immunosuppressive medications for the management of study drug-related AEs • Short-term premedication for patients receiving combinations where the prescribing information for the agent requires the use of steroids for documented hypersensitivity reactions • Use in patients with contrast allergies • In addition, use of inhaled, topical, and intranasal corticosteroids is permitted. A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of non-immunotherapy related events experienced by the patient (eg, chronic obstructive pulmonary disease, radiation, nausea, etc).
Live attenuated vaccines	Prohibited from the time that patients enter the main screening period until 180 days after the last dose of study treatment.
Herbal and natural remedies which may have immune-modulating effects	Should not be given concomitantly unless agreed by the Sponsor

AE adverse event

The use of herbal preparations/medications should be discouraged throughout the study. These herbal medications include, but are not limited to: St. John's Wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone, yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 7 days prior to first dose of study drug (3 weeks for St John's Wort). Use of these products, as well as use of all vitamins, nutritional supplements and all prescribed concomitant medications, must be recorded in the eCRF.

Other concomitant treatment

Medication other than that described above, which is considered necessary for the patient's safety and wellbeing, may be given at the discretion of the Investigator and recorded in the appropriate sections of the eCRF.

6.5.1 Rescue and supportive medication

There is no rescue medication for AZD6738 monotherapy.

Supportive medication, described in Table 4, may be given at the discretion of the Investigator and recorded in the appropriate sections of the eCRF.

Table 4 Supportive medication

Supportive medication/class of drug	Usage
Concomitant medications or treatments (eg, acetaminophen or diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care, except for those medications identified as "prohibited," as listed above	To be administered as prescribed by the Investigator
Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy to non-target lesions, etc])	Should be used, when necessary, for all patients AZD6738 treatment should be discontinued for a minimum of 3 days before a patient undergoes palliative radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.
Inactivated viruses, such as those in the influenza vaccine or authorised and approved COVID-19 vaccines.	Permitted. Administration of COVID-19 vaccines should be avoided for 72 hours prior to administration of the first dose of study treatment.

COVID-19 Coronavirus Disease 2019.

6.5.2 Drug-drug interaction between AZD6738 and other drugs

AZD6738 is an investigational drug for which no data on in vivo interactions are currently available. Potential interaction and guidelines below are considered on the basis of preclinical in vitro data only.

The lists of CYP and transporter inhibitors/inducers, and CYP and transporter substrates are available in Section 11. They are not exhaustive and the absence of a drug from these lists does not imply that its combination with AZD6738 is safe. If AZD6738 is being administered in combination, potential interactions of the combination partner should also be considered.

- **Restrictions regarding drugs affecting CYP metabolism**
  The principal enzyme for metabolising AZD6738 is CYP3A4. Patients should avoid concomitant drugs, herbal supplements, and/or ingestion of foods known to modulate CYP3A4 activity from the time they enter the screening period until 28 days after the last dose of study medication.
  - Prior to study medication, use of potent inducers or inhibitors of CYP3A are not permitted. For patients taking any of these drugs, the required wash-out periods

before starting AZD6738 is five half-lives; except for St. John's wort, which is 3 weeks.

- On study medication, if there is no suitable alternative concomitant medication other than a potent inhibitor of CYP[CCI] the Investigator must interrupt AZD6738 for the duration of the potent CYP[CC] inhibitor and wait for the required wash-out period (five half-lives) before dosing AZD6738 again. If potent CYP[CC] inducers are considered necessary for the patient's safety and welfare, this may diminish the clinical efficacy of AZD6738, and the patient should be monitored carefully for any change in the efficacy of study treatment. Refer to Section 11 for additional guidance.
- The use of any herbal supplements or 'folk remedies' (and medications and foods that significantly modulate CYP[CC] activity) should be discouraged. If deemed necessary, such products may be administered with caution and the reason for use documented in the eCRF.

In vitro data also suggest that AZD6738 may be metabolised by CYP[CCI] to a lesser extent, therefore caution should be applied with co-administration of potent inhibitors or inducers of CYP[CCI] (examples provided in Section 11).

- **Drugs known to be inhibitors or inducers of [CCI] undertake appropriate monitoring if co-administration is necessary**
  - AZD6738 is also a [CCI] substrate. Co-administration of [CCI] inhibitors or inducers may affect exposure to AZD6738 and therefore should not be co-administered with AZD6738. If the use of any inhibitors or inducers of [CCI] are considered necessary for the patient's safety and welfare, the Investigator must interrupt AZD6738 for the duration of the [CCI] inhibitor or inducer and wait for the required wash-out period of the P-gp modulator (five half-lives) before dosing with AZD6738.
  - AZD6738 is a substrate of [CCI]. Co-administration of [CCI] inhibitors or inducers may affect exposure to AZD6738; therefore, it is recommended that the Investigators must interrupt AZD6738 for the duration of the [CCI] inhibitor or inducer and wait for the required wash-out period of the [CCI] modulator (five half-lives) before dosing AZD6738 again.
- **Drugs known to be substrates of CYP[CCI] and/or CYP[CCI] CYP[CCI] and CYP[CCI] undertake appropriate monitoring if coadministration is necessary**
  - AZD6738 is an inducer of CYP[CCI] CYP[CCI] and CYP[CCI] and showed weak inhibition of CYP[CCI] CYP[CCI] and CYP[CCI] Caution should be applied with co-administration of drugs that are either completely metabolised by CYP[CCI] and/or CYP[CCI] CYP[CCI] or CYP[CCI] or that are substrates of CYP[CCI] and/or CYP[CCI] CYP[CCI] and CYP[CCI] and also have a narrow therapeutic index. Investigators should be aware that the exposure of other drugs metabolised by CYP[CCI] CYP[CCI] and/or CYP[CCI] may be increased, and exposure of other drugs metabolised by CYP[CCI] and/or CYP[CCI] may be reduced.

- **Drugs known to be substrates of CCI undertake appropriate monitoring if co-administration is necessary**
  - AZD6738 is an inhibitor of CCI Co-administration of substrates of CCI may affect exposure to AZD6738; therefore, it is recommended that caution should be applied when such drugs are to be administered with AZD6738.
- **Anticoagulation therapy**
  - Patients on warfarin may participate in this study but it is recommended that their INR is monitored more frequently.

6.6 Dose modification and discontinuation

Dose adjustments for AZD6738 will be based on the organ system exhibiting the greatest degree of toxicity. Dose reductions or interruptions, and initiation of supportive care, are allowed as deemed appropriate by the treating physician. The maximum interruption or cycle delay that is permitted is 28 days.

Management of study drug-related toxicities is described in detail in Section 8.4.5.

Table 5 AZD6738 dose modifications for toxicity management

Dose level	AZD6738
Initial dose	240 mg twice daily Days 1-14
Level 1 dose reduction	160 mg twice daily Days 1-14
Level 2 dose reduction	120 mg twice daily Days 1-14
Level 3 dose reduction	80 mg twice daily Days 1-14
Level 4 dose reduction	Stop treatment

Study treatment dose interruption for conditions other than toxicity resolution should be kept as short as possible. If a patient cannot restart study treatment within 4 weeks of the planned onset date, for resolution of intercurrent conditions not related to disease progression or toxicity, the case should be discussed with the AstraZeneca study physician. Any patient requiring a toxicity related dose delay of more than 28 days from the last day of dosing must be discontinued from the study unless there is approval from the study physician for the patient to continue.

All dose reductions and interruptions (including any missed doses), and the reasons for the reductions/interruptions are to be recorded in the eCRF.

Study treatment should be stopped at least 3 days prior to planned surgery. After surgery study treatment can be restarted when the wound has healed. No stoppage of study treatment is required for any biopsy procedure.

Patients who develop an event of ≥ Grade 3 of thrombocytopenia, anaemia, and/or neutropenia later than Cycle 2 in their treatment will need to have additional assessment on Day 8 (± 1 day window) until there is no evidence of ≥ Grade 3 thrombocytopenia, anaemia, and/or neutropenia for at least 2 cycles.

6.7 Treatment after the end of the study

Patients are permitted to either receive standard of care therapy, or to continue to receive study treatment following the end of the study if, in the opinion of the Investigator, they are continuing to receive benefit from treatment. After discontinuation of study treatment, the Investigator will be at liberty to define further most appropriate anti-cancer treatment. Subsequent anti-cancer treatment is expected to be initiated following the cancer recurrence or development of a new cancer. Information on subsequent anti-cancer therapies should be recorded on the clinical database.

7. DISCONTINUATION OF TREATMENT AND PATIENT WITHDRAWAL

Please refer to Section 7 in the core protocol. Stopping criteria for AZD6738 are in Section 8.4.5 of this module.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in the SoA (Table 1).

8.1 Efficacy assessments

Please refer to the core protocol.

8.2 Safety assessments

8.2.1 Clinical safety laboratory assessments

Please refer to core protocol.

8.2.1.1 Coagulation

Please refer to core protocol.

8.2.1.2 Other safety assessments

Please refer to core protocol.

8.2.1.3 Pneumonitis (interstitial lung disease) investigation

The following assessments, and additional assessments if required, will be performed to enhance the investigation and diagnosis of potential cases of pneumonitis. The results of the assessment will be collected.

- Physical examination; Signs and symptoms (cough, shortness of breath and pyrexia, etc) including auscultation for lung field will be assessed.
- SpO_2; Saturation of peripheral oxygen (SpO_2)
- Other items; When pneumonitis (interstitial lung disease [ILD]) is suspected during study treatment, the following markers should be measured where possible:
  - ILD markers (KL-6, SP-D) and β-D-glucan
  - Tumour markers: Particular tumour markers which are related to disease progression.

8.2.2 Physical examinations

Please refer to core protocol.

8.2.3 Vital signs

Please refer to Section 8.2.3 in the core protocol. However, if clinically indicated, eg, in the event of clinically relevant symptoms such as pre-syncope or dizziness, blood pressure will be measured in the supine and standing positions after at least 10 minutes' rest. Assessments will be performed at the visits as shown in the SoA (Table 1).

8.2.4 Electrocardiograms

Please refer to core protocol.

8.2.5 Performance status

Please refer to core protocol.

8.3 Collection of adverse events

Please refer to the core protocol.

8.4 Safety reporting and medical management

8.4.1 Reporting of serious adverse events

Please refer to the core protocol.

Any myeloid malignancies (ie., MDS and/or AML) should be reported whenever this has been observed in the follow-up of the patients.

8.4.2 Pregnancy

Please refer to the core protocol.

8.4.3 Overdose

Please refer to the core protocol.

8.4.4 Medication error

Please refer to the core protocol.

8.4.5 Management of study drug-related toxicities

If a patient experiences a clinically significant and/or unacceptable toxicity dosing will be interrupted and supportive therapy administered as required.

If the toxicity resolves or reverts to CTCAE v4.03 Grade ≤ 1or 2 (depending on the toxicity), treatment with AZD6738 may be restarted using the rules in Table 6 for dose modifications. Patients who are at the lowest possible dose, or who had their dose previously reduced to the lowest possible dose and who have demonstrated an acceptable response to the dose interruption may be permitted to restart at the lowest dose level at the discretion of the Investigator.

If the toxicity does not resolve to CTCAE Grade ≤ 1 or 2 or the patient is not showing clinical benefit, then the patient should be discontinued from treatment and observed until resolution of the toxicity.

Any patient requiring a toxicity related dose delay of more than 28 days from the last day of dosing must be discontinued from the study unless there is approval from the study physician for the patient to continue.

If a patient develops severe haematologic toxicity or blood transfusion dependence, treatment with AZD6738 should be interrupted and appropriate haematologic testing should be initiated. If the blood parameters remain clinically abnormal after 4 weeks of AZD6738 dose interruption, bone marrow analysis and/or blood cytogenetic analysis are recommended. If myeloid malignancies are confirmed whilst on treatment with AZD6738, it is recommended that AZD6738 should be discontinued and the patient be treated appropriately. AEs of myeloid malignancies should be monitored by conventional AE collection and reporting, additionally any cases should be reported after the 30-day follow-up period irrespective of Investigator causality.

The dose of AZD6738 must not be adjusted under any other circumstances than those described in this section unless prior agreement is given by the Sponsor.

All dose modifications and interruptions (including any missed doses) and the reasons for the modifications/interruptions are to be recorded in the eCRF.

Table 6 Dose interruption and stopping criteria (14-day schedule)

Event	Action
Grade 1 neutropenia and/or thrombocytopenia	AZD6738 dosing may continue if neutrophil count is ≥ 1500/mm^3 and/or platelet count is ≥ 75000/mm^3.
Grade 1-2 toxicities (except neutropenia and thrombocytopenia)	Investigator decision whether to interrupt AZD6738 (max 28 days) or continue treatment. Treatment may be resumed at the same dose level or with a dose reduction by 1 level.
Grade 2 neutropenia or Grade 3 anaemia	Interrupt AZD6738 (max 28 days) and give appropriate supportive treatment eg, transfusion, until AE improves to at least neutrophil count ≥ 1500/mm^3 and haemoglobin ≥ 8.0 g/dL, then restart reducing the dose of AZD6738 by 1 level[a]. If a further dose reduction is required after the level 3 dose reduction, the patient must stop treatment.
Grade 2-3 thrombocytopenia	**First occurrence** Interrupt AZD6738 only (max 28 days) and give appropriate supportive treatment until platelets improve to at least ≥100000/mm^3. At resolution, it is not mandatory to lower the dose as blood counts may recover during the "off period" on the intermittent schedule. If blood counts do not recover by the start of the next dosing period, AZD6738 should be restarted with a dose reduction by 1 level[a] for AZD6738. **Subsequent occurrences** Interrupt AZD6738 only (max 28 days) and give appropriate supportive treatment. Treatment may be restarted with a reduced dose of AZD6738 when the toxicity is resolved, or treatment may be stopped at the Investigator's discretion.
Grade 4 thrombocytopenia	Interrupt AZD6738 (max 28 days) and give appropriate supportive treatment; Investigator discretion on whether to restart treatment with a dose reduction by 1 dose level[a] for AZD6738 when the platelet count has recovered to ≥ 100000/mm^3 or stop treatment.
Grade 3-4 toxicity (including Grade 3-4 neutropenia or Grade 4 anaemia) *Excludes* Grade 3 anaemia or Grade 3-4 thrombocytopenia (see above)	**First occurrence** Interrupt AZD6738 (max 28 days) and give appropriate supportive treatment; restart treatment with a dose reduction by 1 level[a] for AZD6738 when the toxicity is resolved (Grade 1 or 2 depending on the toxicity or returns to baseline). **Subsequent occurrences** Investigator discretion on whether to interrupt AZD6738 (max 28 days) or to stop treatment. Restart treatment with an AZD6738 dose reduction of 1 or 2 levels. If a further dose reduction is required after the level 3 dose reduction, the patient must stop treatment.
Vomiting	If vomiting occurs shortly after AZD6738 is swallowed, the dose should only be replaced if all of the intact tablets can be counted. Resume with the following scheduled dose.

Table 6 Dose interruption and stopping criteria (14-day schedule)

Event	Action
Missed dose	Allowed to take the scheduled dose up to 2 hours after the scheduled dose time. If greater than 2 hours, the missed dose should not be taken and the patient should continue with next dose at the allotted time.

[a] This table is for guidance. Therefore, for example, it may be deemed appropriate by the Investigator to reduce the dose by more than one dose level depending on the individual patient circumstances.

Individual stopping criteria:

Hepatic

- ALT or AST or ALP* > 5 × ULN
- ALT or AST or ALP* > 3 × ULN with the appearance of symptoms associated with a clinical diagnosis of hepatitis including right upper quadrant pain or tenderness, fever, rash or eosinophilia (> 5%)
- [ALT or AST > 3 × ULN] and [total bilirubin > 2 × ULN or INR+ >1.5 or other evidence of impairment to the synthesis function of the liver]

* In the presence of bone metastasis, assess bone specific isoform of raised ALP in the presence of a raised gamma-glutamyltransferase (to ensure the ALP change is specific to the liver).

\+ Unless patient is receiving warfarin.

Please refer to Appendix E "Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law".

Cardiovascular

Clinically significant hypotension defined as an asymptomatic decrease of more than 20 mmHg in systolic blood pressure to below 70 mmHg persisting for at least 10 minutes.

Symptomatic orthostatic fall in systolic blood pressure of more than 20 mmHg compared to resting supine systolic blood pressure.

Haematologic

Patients with suspected or with indications of MDS and/or AML must have the dose of AZD6738 stopped under all circumstances, and evidence of AML/MDS should be ruled out. Further treatment can only be accepted after discussion and agreement with the sponsor.

8.5 Pharmacokinetics

Refer to the core protocol.

8.6 Pharmacodynamics

Pharmacodynamic parameters will be evaluated in this study (see Section 8.6 of the core protocol).

8.7 Genetics

Refer to the core protocol.

8.8 Biomarkers

Refer to the core protocol.

8.9 Medical Resource Utilisation and Health Economics

Medical Resource Utilisation and Health Economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

Refer to the core protocol.

10. REFERENCES

Cimprich and Cortez 2008
Cimprich KA, Cortez D. ATR: an essential regulator of genome integrity. Nat Rev Mol Cell Biol. 2008;9:616-27.

De Bono et al 2019
De Bono JS, Tan DSP, Caldwell R, Terbuch A, Goh BC, Heong V et al. First-in-human trial of the oral ataxia telangiectasia and Rad3-related (ATR) inhibitor BAY 1895344 in patients (pts) with advanced solid tumors. J Clin Oncol. 2019;37(15) suppl:3007.

Galluzzi et al 2012
Galluzzi L, Senovilla L, Zitvogel L, Kroemer G. The secret ally: immunostimulation by anticancer drugs. Nat Rev Drug Discov. 2012;11(3):215-33

Krebs et al 2018
Krebs MG, Lopez J, El-Khoueiry A, Bang Y-J, Postel-Vinay S, Abida W et al. Abstract CT026: Phase I study of AZD6738, an inhibitor of ataxia telangiectasia Rad3-related (ATR), in combination with olaparib or durvalumab in patients (pts) with advanced solid cancers. AACR Proceedings. 2018;78(13) Supplement. DOI: 10.1158/1538-7445.AM2018-CT026.

Min et al 2017
Min A, Im S-A, Jang H, Kim S, Lee M, Kim DK et al. AZD6738, A Novel Oral Inhibitor of ATR, Induces Synthetic Lethality with ATM Deficiency in Gastric Cancer Cells. Mol Cancer Ther. 2017;16(4);566–77.

O'Connor 2015
O'Connor MJ. Targeting the DNA Damage Response in Cancer. Mol Cell. 2015;60:547-60.

Reaper et al 2011
Reaper PM, Griffiths MR, Long JM, Charrier J-D, Maccormick S, Charlton PA et al. Selective Killing of ATM- Or p53-deficient Cancer Cells Through Inhibition of ATR. Nat Chem Biol. 2011;7(7):428-30.

Stewart et al 2015
Stewart R, Morrow M, Hammond SA, Mulgrew K, Marcus D, Poon E et al. Identification and characterization of MEDI4736, an antagonistic anti-PD-L1 monoclonal antibody. Cancer Immunol Res. 2015;3(9):1052-62.

Toledo et al 2011
Toledo LI, Murga M, Zur R, Soria R, Rodriguez A, Martinez S et al. A cell-based screen identifies ATR inhibitors with synthetic lethal properties for cancer-associated mutations. Nat Struct Mol Biol. 2011;18:721-7.

Vendetti et al 2015
Vendetti FP, Lau A, Schamus S, Conrads TP, O'Connor MJ, Bakkenist CJ. The orally active and bioavailable ATR kinase inhibitor AZD6738 potentiates the anti-tumor effects of cisplatin to resolve ATM-deficient non-small cell lung cancer in vivo. Oncotarget. 2015;6(42):44289-44305.

Villaruz et al 2016
Villaruz LC, Jones H, Dacic S, et al. ATM protein is deficient in over 40% of lung adenocarcinomas. Oncotarget. 2016;7(36):57714-57725.

Weber and Ryan 2015
Weber AM, Ryan AJ. ATM and ATR as therapeutic targets in cancer. Pharmacol Ther. 2015;149:124-38.

11. AZD6738 DRUG-DRUG INTERACTIONS

Restrictions regarding drugs affecting CYPCC metabolism

There are currently no data confirming that there is a pharmacokinetic (PK) interaction between drugs that affect CYPCC metabolism and AZD6738; a potential interaction is considered on the basis of preclinical and in vitro data only. AZD6738 is predominantly eliminated via CYPCC metabolism, therefore CYPCC inhibitors or inducers may increase or decrease exposure to AZD6738, respectively. Potent inhibitors or inducers of CYPCC should not be combined with AZD6738. In vitro data also suggest that AZD6738 may be metabolised by CYPCCI to a lesser extent, therefore caution should be applied with co-administration of potent inhibitors or inducers of CYPCCI.

Drugs known to be inhibitors and inducers of CYPCC or CYPCCI are listed in Table 7 and Table 8, respectively. These lists are not intended to be exhaustive, and similar restrictions will apply to other agents that are known to modulate CYPCC or CYPCCI activity. Please contact AstraZeneca with any queries on this issue. Please refer to full prescribing information for all drugs prior to co-administration with AZD6738.

Table 7 Drugs known to be inhibitors and inducers of CYP[redacted]

Potent CYP3A inhibitors	Potent CYP[redacted] inducers
boceprevir	apalutamide
ceritinib	avasimibe
clarithromycin	carbamazepine
cobicistat (GS-9350)	ceralasertib
conivaptan	enzalutamide
danoprevir / RIT	ivosidenib
elvitegravir / RIT	lumacaftor
grapefruit juice[a]	mitotane
idelalisib	phenobarbital
indinavir	phenytoin
indinavir /RIT	rifampin
itraconazole	rifapentine
ketoconazole	St John's Wort extract
LCL161	
lopinavir / RIT	
mibefradil	
mifepristone	
nefazodone	
nelfinavir	
posaconazole	
ribociclib	
ritonavir	
saquinavir	
saquinavir / RIT	
telaprevir	
telithromycin	
tipranavir/RIT	
troleandomycin	
VIEKIRA PAK2[b]	
voriconazole	

[a] Double-strength grapefruit juice. Patients should abstain from eating large amounts of grapefruit and Seville oranges (and other products containing these fruits eg, grapefruit juice or marmalade) during the study (eg, no more than a small glass of grapefruit juice (120 mL) or half a grapefruit or 1 to 2 teaspoons (15 g) of Seville orange marmalade daily.

[b] VIEKIRA PAK = 150/100 mg paritaprevir/ritonavir + 25 mg ombitasvir + 800 mg dasabuvir for 28 days.

List created using the University of Washington Drug-Drug Interaction Database July 2019.

RIT Ritonivir. Ritonavir has dual effects of simultaneous CYP[redacted] inhibition and induction, and the net pharmacokinetic outcome during chronic ritonavir therapy is inhibition of CYP[redacted] activity

Table 8 Drugs known to be inhibitors and inducers of CYP[redacted]

Potent CYP[redacted] inhibitors	**Potent CYP[redacted] inducers**
gemfibrozil clopidogrel	None identified

List created using the University of Washington Drug-Drug Interaction Database Jan 2020.

Drugs known to be inhibitors or inducers of [redacted] undertake appropriate monitoring if co-administration is necessary

AZD6738 is a substrate of [redacted] Co-administration of [redacted] inhibitors/inducers or [redacted] inhibitors/inducers may affect exposure to AZD6738, therefore it is recommended that these are not co-administered with AZD6738.

Drugs known to be inhibitors or inducers of [redacted] are listed in Table 9 and Table 10, respectively. These lists are not intended to be exhaustive, and similar restrictions will apply to other agents that are known to modulate [redacted] Please contact AstraZeneca with any queries on this issue. Please refer to full prescribing information for all drugs prior to co-administration with AZD6738.

Table 9 Drugs known to be inhibitors or inducers of CCI

Drugs Known to be Inhibitors of CCI	Drugs Known to be Inducers of CCI
alogliptin	apalutamide
amiodarone	avasimibe
asian ginseng (Panax ginseng)	carbamazepine
asunaprevir	danshen (Salvia miltiorrhiza)
AZD5672	efavirenz
azithromycin	genistein
canagliflozin	green tea
captopril	phenytoin
carvedilol	quercetin
clarithromycin	rifabutin
clopidogrel	rifampin
cobicstat	ritonavir
conivaptan	St. John's wort extract
cremophor EL	tivantinib
cremophor RH	
curcumin	
daclatasvir	
daclatasvir/asunaprevir/beclabuvir	
diltiazem	
diosmin	
dronedarone	
elagolix	
eliglustat	
erythromycin	
felodipine	
five-flavor berry (schisandra chinensis)	
flibanserin	
fluvoxamine	
fostamatinib	
ginkgo	
glecaprevir/pibrentasvir	
indinavir	
indinavir/ritonavir	
isavuconazole	
itraconazole	
ivacaftor	
ketoconazole	
lapatinib	
lopinavir/ritonavir	
mibefradil	

mifepristone	
milk thistle	
mirabegron	
nelfinavir	
neratinib	
nifedipine	
nitrendipine	
osimertinib	
paritaprevir/ritonavir/ombitasvir	
paroxetine	
piperine	
propafenone	
quercetin	
quinidine	
quinine	
ranolazine	
rifampin	
ritonavir	
rolapitant	
rucaparib	
saquinavir/ritonavir	
sarecycline	
simeprevir	
sofosbuvir/velpatasvir/voxilaprevir	
St. John's wort extract	
surfactant TPGS	
suvorexant	
talinolol	
telithromycin	
telaprevir	
telmisartan	
tezacaftor/ivacaftor	
ticagrelor	
tipranavir/ritonavir	
tolvaptan	
valbenazine	
valspodar (PSC 833)	
vandetanib	
velpatasvir	
vemurafenib	
verapamil	
voclosporin	

vorapaxar	

List created using the University of Washington Drug-Drug Interaction Database October 2019.

Table 10 Drugs known to be inhibitors or inducers of CCI

Drugs Known to be Inhibitors of CCI	Drugs Known to be inducers of CCI
afatinib aripiprazole curcumin cyclosporine elacridar erlotinib fluvastatin fumitremorgin gefitinib ivermectin lapatinib nilotinib novobiocin pantoprazole pitavastatin ponatinib quercetin quizartinib rabeprazole regorafenib rilpivirine sulfasalazine sunitinib tacrolimus teriflunomide trametinib trifluoperazine vismodegib eltrombopag atazanavir lopinavir ritonavir tipranavir omeprazole estrone 17b-estradiol imatinib mesylate	Please check individual drugs on a case-by-case basis

List created using http://dmd.aspetjournals.org/content/dmd/43/4/490.full.pdf
Note: Although CCI is involved in a number of clinically relevant DDIs, none of the listed inhibitors above is truly specific for this transporter

Drugs known to be substrates of CYP[CCI] and/or CYP[CCI] or CYP[CCI] or CYP[CCI] undertake appropriate monitoring if co-administration is necessary

AZD6738 is an inducer of CYP[CCI] CYP[CCI] and CYP[CCI] and showed weak inhibition of CYP[CCI] CYP[CCI] and CYP[CCI]. Therefore, caution should be applied with co-administration of drugs that are either completely metabolised by CYP[CCI] and/or CYP[CCI] or CYP[CCI] or CYP[CCI] or that are substrates of CYP[CCI] and/or CYP[CCI] CYP[CCI] and CYP[CCI] and also have a narrow therapeutic index (Table 11). Investigators should be aware that the exposure of other drugs metabolised by CYP[CCI] CYP[CCI] and/or CYP[CCI] may be increased, and exposure of other drugs metabolised by CYP[CCI] and/or CYP[CCI] may be reduced.

Table 11 Drugs known to be metabolised by CYP[CCI] and/or CYP[CCI] CYP[CCI] and CYP[CCI]

Metabolised by CYP[CCI]	Metabolised by CYP[CCI]	Metabolised by CYP[CCI]	Metabolised by CYP[CCI]
Abemaciclib (NTR)	agomelatine	daprodustat	benzbromarone
ABT-384	alosetron[a]	dasabuvir	celecoxib
Acalabrutinib (NTR)	caffeine	repaglinide[b]	ibuprofen
alfentanil	duloxetine		(R)-ibuprofen
alisporivir	melatonin		(S)-ibuprofen
almorexant	pirfenidone		glimepiride
alpha-dihydroergocryptine	ramelteon[a]		glipizide
aplaviroc	selegiline[a]		lornoxicam
aprepitant	tacrine		meloxicam
asunaprevir	tasimelteon[a]		piroxicam
atazanavir	tizanidine (NTR)		(S)-warfarin (NTR)
atorvastatin			tolbutamide
avanafil			
avapritinib			
AZD1305			
BIRL 355			
blonanserin			
bosutinib (NTR)			
brecanavir			
brotizolam			
budesonide			
buspirone			
BZF961			
capravirine			
casopitant			
cobimetinib (NTR)			
conivaptan (NTR)			
danoprevir			

darifenacin darunavir dasatinib (NTR) dronedarone ebastine eletriptan eliglustat (in subjects CYP[redacted] PMs) elvitegravir entrectinib (NTR) eplerenone everolimus felodipine ibrutinib indinavir isavuconazole itacitinib ivabradine ivacaftor L-771,688 Levomethadyl/Levacetymethadol (LAAM) (NTR) Lomitapide (NTR) lonafarnib lopinavir lovastatin lumefantrine lurasidone maraviroc midazolam midostaurin (NTR) morphothiadin naloxegol neratinib (NTR) nisoldipine paritaprevir4 perospirone pyrotinib quetiapine ridaforolimus saquinavir sildenafil			

simeprevir			
simvastatin			
sirolimus			
tacrolimus			
terfenadine			
ticagrelor			
tilidine3			
tipranavir			
tolvaptan (NTR)			
triazolam			
ubrogepant			
ulipristal			
vardenafil			
venetoclax (NTR)			
vicriviroc			
vilaprisan			
voclosporin			
zanubrutinib (NTR)			

[a] Complex Interaction -Substrates metabolized by multiple enzymes, including CYP CCI.
[b] Repaglinide is also a substrate of CCI, which might also be inhibited by gemfibrozil or its glucuronide.

List created using the University of Washington Drug-Drug Interaction Database August 2021. Note: This is not an exhaustive list.
(NTR) drug listed in the Narrow Therapeutic Index list by CYP isoform in DrugBank.

Drugs known to be substrates of CCI undertake appropriate monitoring if co-administration is necessary

AZD6738 is also an inhibitor of CCI. Caution should be applied with co-administration of substrates of CCI as AZD6738 may increase their exposure.

Drugs known to be substrates of CCI are listed in Table 12 and Table 13, respectively. These lists are not intended to be exhaustive and appropriate medical judgment is required. Please contact AstraZeneca with any queries on this issue. Please refer to full prescribing information for all drugs prior to co-administration with AZD6738.

Table 12 Drugs known to be substrates of [redacted]

docetaxel
enalapril
olmesartan
phalloidin
repaglinide
statins[a]
temocaprilat
valsartan

[a] All statins

List created using https://www.solvobiotech.com/transporters/[redacted], latest access Nov 2019

Table 13 Drugs known to be substrates of [redacted]

anthracyclines
chlorothiazide
daunorubicin
doxorubicin
imatinib
irinotecan
methotrexate
mitoxantrone
nucleoside analogs
pantoprazole
prazosin
SN-38
topotecan
teriflunomide
rosuvastatin

List created using https://www.solvobiotech.com/transporters[redacted], latest access Nov 2019

Clinical Study Protocol	
Drug Substance	Umbrella study
Study Code	D6185C00001 (HUDSON)
Version	14.0
Date	09 October 2024

Appendix Q

Module 9: Durvalumab plus AZD6738 (ceralasertib)

An Open-Label, Multi-Drug, Biomarker-Directed, Multi-Centre Phase II Umbrella Study in Patients with Non-Small Cell Lung Cancer, who Progressed on an Anti-PD-1/PD-L1 Containing Therapy (HUDSON)

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

Regulatory Agency Identification Numbers:

EudraCT number: 2017-002208-28

EU CT number: 2023-509004-15-00

IND number: 138050

VERSION HISTORY

Version 14.0, 09 October 2024
Key amendments and rationale for changes: **Section 2.2.3.1, emerging data from module 3 of HUDSON:** CCI [redacted] when AZD6738 is used as monotherapy and in combination with durvalumab. **Table 2, study drug:** removed reference to Annex 13. **Section 6.5.2, Effect of AZD6738 on other drugs; Section 11, AZD6738 drug-drug interactions:** Updated to describe AZD6738 as an inducer of CYPCCI CYPCCI and CYPCCI and a weak inhibitor of CYPCCI and CYPCCI **Section 8.4.1, reporting of serious adverse events:** addition of text relating to the reporting of MDS and/or AML during follow-up. **Section 8.4.5.2, management of AZD6738-related toxicities:** • Guidance was added for patients who experience suspected MDS/AML. • New sub-section was added to describe actions to be taken if a patient displays suspected indications of MDS and/or AML. **Table 7, drugs known to be inhibitors and inducers of CYPCC:** Ceralasertib was added as a potent CYPCC inducer. Minor text clarifications were also made.

Version 13.0, 14 December 2023
Key amendments and rationale for changes: **Front page:** EU CT number has been added in line with the core CSP. **Section 6.1.1, study drugs:** Text regarding 'Packaging and Labelling' updated to remove the information that labels will fulfil GMP Annex 13 requirements for labelling, as this Annex has been replaced.

Version 12.0, 01 March 2023
Key amendments and rationale for changes: **Section 6.2, preparation/handling/storage/accountability:** Added a reference to the Pharmacy Manual.

Version 11.0, 16 August 2022
Key amendments and rationale for changes: **Table 1, schedule of activities:** • Removal of CCI sample collection Day 15 and Day 22 (Cycles 1 and 2), text related to collection days for subsequent cycles and footnote added to clarify timing of sample collection. This change is made to align with other AstraZeneca projects. • Addition of footnote to clarify an on-treatment biopsy is not required if a fresh tumour sample is not collected at pre-screening. Analysis requires a baseline result for comparison (ie, from the pre-screening sample). **Section 6.2.3, storage:** Text is updated to clarify monitoring of temperature refers to study drug (durvalumab) storage.

Version 10.0, 12 April 2022
Key amendments and rationale for changes: **As of implementation of protocol v10.0, patient recruitment to Module 9 is closed:** Text added to Section 2, introduction and Section 4.1, overall design. **Table 1, schedule of activities:** • Addition of footnote to clarify the activities for patients continuing on study treatment after the data cut-off for the module clinical study report. • Blood sample for PBMCs for flow cytometry label clarified. • Additional blood sample at Cycle 2 Day 22 visit included for the following assessments: circulating soluble factors, gene expression, immunophenotyping, and TCR immuno-sequencing. To monitor pharmacodynamic activity of AZD6738 and durvalumab. • Blood sample for CCI assessments moved from Cycle 2 Day 15 to Cycle 2 Day 22 to align with other biomarker blood sample collections.

- Additional blood sample at study drug discontinuation visit included for the following assessments: Immunophenotyping and TCR immuno-sequencing. To evaluate immune phenotype status at discontinuation of study drug.

Figure 1, study design: Addition of footnote to clarify survival follow-up of screen failures is no longer required as of implementation of protocol v10.0.

Section 2.2, background: Reference to approval of durvalumab for the treatment of urothelial carcinoma in the US removed due to voluntary withdrawal of this indication in this country. Text also added to clarify the weight-based regimen (10 mg/kg every 2 weeks) is approved for urothelial carcinoma.

Section 2.2.1.2, durvalumab data: Number of patients treated with durvalumab updated to align with durvalumab IB Edition 17.

Section 2.2.2.2, AZD6738 clinical programme: Text updated to align with AZD6738 IB Edition 10 and reference to current IB added.

Section 2.2.3, Durvalumab and AZD6738 in combination; Section 4.3.2, justification for AZD6738 dose: Sentence added for the recommended Phase II dose from Study D553000004 Module 3.

Section 4.3.2, justification for AZD6738 dose: Safety data for the AZD6738 plus durvalumab dosing schedule updated per the AZD6738 IB Edition 10 in response to a CCI

Section 5.3.1, restrictions applicable to durvalumab; Table 4, supportive medication: Text added to provide guidance for the use and timing of authorised and approved COVID-19 vaccines, to align with the COVID-19 vaccination guidance letter (dated 24 February 2021) provided to sites. Test for live attenuated vaccines also amended for clarification.

Section 6.2.2, study drug administration: Text amended to clarify AZD6738 can only be given without durvalumab if durvalumab is permanently stopped.

Table 4, supportive medication:

- Text added to clarify when AZD6738 treatment should be discontinued and restarted before and after a patient undergoes palliative radiation treatment. To align with the Ceralasertib Project Specific Safety Requirements v14.

Section 6.5.2 effect AZD6738 on other drugs and Section 11, AZD6738 drug-drug interactions: Text and associated tables updated per the Ceralasertib Project Specific Safety Requirements v 14.

Section 6.6, dose modification and discontinuation:

- Text (and cross reference to Section 7.1.1 of the core protocol) added to clarify that a patient may continue on monotherapy if the other treatment is permanently stopped.
- Text added to describe when study treatment should be stopped in relation to planned surgery, to align with Module 8 and the Ceralasertib Project Specific Safety Requirements v14.

Table 6, dose interruption and stopping criteria: To align with the Ceralasertib Project Specific Safety Requirements v14, the table title and text for Grade 1-2 toxicities were updated.

Section 8.6, pharmacodynamics: Text updated to clarify pharmacodynamic parameters will be evaluated in the study and a cross reference to Section 8.6 of the core protocol added.

Version 9.0, 14 May 2021

Key amendments and rationale for changes:
Revisions to Module 9 are described in the version history of Version 8.1 and Version 9.0 of Module 9. Please refer to both sections of the version history for a complete summary of changes.

Additional safety assessments have been added based on reported adverse events of Grade ≥ 3 haematological toxicity including: anaemia, thrombocytopenia, neutropenia (including a Grade 3 febrile neutropenia in one patient) in 4 patients, out of a total of 8 patients, who received AZD6738 at the 240 mg BD dose (2 weeks on and 2 weeks off in a 4-week cycle) across 2 ongoing AZ sponsored studies, as of 15APR21 (PLANETTE [D5339C00001; n=3 of 4 patients]) and HUDSON [Module 8 and Module 9; n=1 of 4 patients]).

Further details are summarised in the Urgent Safety Measure notification (22APR2021) and Investigator letters (15APR21, 16APR21, and 14MAY21).

Schedule of Activities (Table 1):

- Anaemia and/or neutropenia have been added to the Grade ≥3 haematological toxicities that would necessitate additional safety visits and assessments.

Section 6.6 Dose modification:

- Section updated to add that patients who develop an event of ≥ Grade 3 of thrombocytopenia, anaemia, and/or neutropenia later than Cycle 2 in their treatment will need to have additional assessment on Day 22 (± 1 day window) until there is no evidence of ≥ Grade 3 thrombocytopenia, anaemia, and/or neutropenia for at least 2 cycles.

Version 8.1, 28 April 2021

Key amendments and rationale for changes:

Schedule of Activities (Table 1):

- Additional haematology and clinical chemistry monitoring visits have been added on Day 22 (± 1 day window) of Cycles 1 and 2 to monitor toxicity, with the possibility of including the additional haematology and clinical chemistry monitoring visits in subsequent cycles later in treatment, as clinically indicated.

  This measure is based on investigator-reported adverse events of Grade ≥ 3 haematological toxicity including: anaemia, thrombocytopenia, neutropenia (including febrile neutropenia in one patient) in 4 patients who received AZD6738 in the HUDSON study, and in 4 patients who received AZD6738 in the AstraZeneca-sponsored PLANETTE study (Study D5339C00001) as of the data-cut-off date 14APR2021.

  While anaemia and thrombocytopenia are considered expected events for AZD6738 monotherapy (per the reference safety information (Section 5.6 of the AZD6738 Investigator's Brochure [Edition 9.0]), as these events occurred early after study/cohort initiation, AstraZeneca has taken the decision to introduce additional safety monitoring visits as a precautionary measure.

Section 2.2.3.1 (Emerging data from Module 3 of HUDSON and rationale for assessing AZD6738 monotherapy in Module 8):

- Emerging data up to the data-cut-off-date of 26JAN21 added from Module 3 of HUDSON.

Section 6.6 (Dose Modification and Discontinuation)

- The maximum interruption or cycle delay has been extended from 28 days to 42 days to permit a delay in the onset of the AZD6738 dosing. The change is to ensure that there are correct re-treatment conditions for AZD6738.

Version 8.0, 11 September 2020

Initial Creation

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

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1. PROTOCOL SUMMARY

1.1 Schedule of Activities (SoA)

The Schedule of Activities (SoA) for the on-treatment period for Module 9 is shown in Table 1 below. For the SoA for the pre-screening and main screening visits, please refer to the core protocol.

Table 1 Schedule of Activities – Treatment Intervention Period (Module 9)

	C1 28 days Weeks 1-4			C2 28 days Weeks 5-8			C3 - etc All cycles 28 days			Study drug disc. (28 days after study drug disc.)	Safety follow-up (90 days after study drug disc.)	Survival follow up	Notes
Week	**1**	**3**	**4**	**5**	**7**	**8**	**9, 13, 17 etc**						
Day of cycle	**1[a]**	**15**	**22**	**1**	**15**	**22**	**1**	**15[b]**	**22[e]**				
Window (days)	**0**	**± 2**	**±1**	**± 2**	**± 2**	**±1**	**± 2**	**± 2**	**±1**	**± 7**	**± 7**	**± 7**	
Study procedures[h]													
Physical examination	X	X (if clinically indicated)		X	X (if clinically indicated)		X	X (if clinically indicated)		X			Section 8.2.2 (core CSP)
Vital signs[c]	X	X	X	X	X	X	X	X	X	X			Section 8.2.3
ECG	X			X			X						Section 8.2.4 (core CSP)
Concomitant medications	X	X	X	X	X	X	X	X	X	X			Section 6.5
Laboratory assessments[h]													
Clinical chemistry	X	X	X[d]	X	X	X[d]	X	X	X	X			Section 8.2.1 (core CSP)
Haematology	X	X	X[d]	X	X	X[d]	X	X	X	X			
APTT and INR	X	As clinically indicated											
TSH, free T_3 and free T_4	X	X		X	X		X	X		X			
Urinalysis	X	As clinically indicated											
Pregnancy test	X			X			X			X			Section 8.2.1.2 (core CSP)

	C1 28 days Weeks 1-4			C2 28 days Weeks 5-8			C3 - etc All cycles 28 days			Study drug disc. (28 days after study drug disc.)	Safety follow-up (90 days after study drug disc.)	Survival follow up	Notes
Week	**1**	**3**	**4**	**5**	**7**	**8**	**9, 13, 17 etc**						
Day of cycle	**1[a]**	**15**	**22**	**1**	**15**	**22**	**1**	**15[b]**	**22[e]**				
Window (days)	**0**	**± 2**	**±1**	**± 2**	**± 2**	**±1**	**± 2**	**± 2**	**±1**	**± 7**	**± 7**	**± 7**	
AE/SAE	X	X	X	X	X	X	X	X	X	X	X		Section 8.3 (core CSP)
Study drug administration[h]													
Durvalumab	X			X			X						Section 6.1
AZD6738[f]		X D15-28			X D15-28			X D15 to 28					Section 6.1
Drug accountability				X			X			X			Section 6.2.4
Other administration													
Blood for [redacted] assessments[i]	X			X			X			X			Section 8.8 (core CSP)
Circulating soluble factors	X	X		X		X	X (Cycle 4 only)			X			Section 8.8 (core CSP)
Whole blood for gene expression (PAXgene RNA tubes)	X	X		X		X	X (Cycle 4 only)			X			Section 8.8 (core CSP)
PBMCs for flow cytometry (immunophenotyping activation by / PD-1 CD8+)	X	X		X		X	X (Cycle 4 only)			X			Section 8.8 (core CSP)
TCR immuno-sequencing	X	X		X		X	X (Cycle 4 only)			X			Section 8.8 (core CSP)

	C1 28 days Weeks 1-4			**C2** 28 days Weeks 5-8			**C3 - etc** **All cycles** **28 days**			**Study drug disc.** (28 days after study drug disc.)	**Safety follow-up** (90 days after study drug disc.)	**Survival follow up**	**Notes**
Week	**1**	**3**	**4**	**5**	**7**	**8**	**9, 13, 17 etc**						
Day of cycle	**1[a]**	**15**	**22**	**1**	**15**	**22**	**1**	**15[b]**	**22[c]**				
Window (days)	**0**	**± 2**	**±1**	**± 2**	**± 2**	**±1**	**± 2**	**± 2**	**±1**	**± 7**	**± 7**	**± 7**	
Blood sample for ADA for durvalumab (pre-dose except at safety follow up)	X			X			X (C5D1) then Q12W in first year, then Q24W in second year				X		Section 8.5.3 (core CSP)
Tumour evaluation (CT or MRI, RECIST 1.1)				Every 6 weeks ± 1 week for the first 24 weeks relative to the start of combination therapy (Cycle 1 Day 1), then every 8 weeks ± 1 week thereafter, until objective disease progression as defined by RECIST 1.1 and confirmed with a subsequent scan (in the absence of clinically significant deterioration)									Section 8.1 (core CSP)
Biopsy on treatment (mandatory)[j]					X								Section 8.8 (core CSP). This should align with the first RECIST assessment
Biopsy on disease progression										X			Section 8.8 (core CSP)
Subsequent cancer therapy											X	X	Section 8.1.3.1 (core CSP). Every 3 months

	C1 28 days Weeks 1-4			**C2** 28 days Weeks 5-8			**C3 - etc** **All cycles** **28 days**			**Study drug disc.** (28 days after study drug disc.)	**Safety follow-up** (90 days after study drug disc.)	**Survival follow up**	**Notes**
Week	**1**	**3**	**4**	**5**	**7**	**8**	**9, 13, 17 etc**						
Day of cycle	**1[a]**	**15**	**22**	**1**	**15**	**22**	**1**	**15[b]**	**22[e]**				
Window (days)	**0**	**± 2**	**±1**	**± 2**	**± 2**	**±1**	**± 2**	**± 2**	**±1**	**± 7**	**± 7**	**± 7**	
Survival status												X[g]	Section 8.1.3.1 (core CSP). Every 3 months

[a] Every effort should be made to minimise the time between allocation and starting treatment. Note, if main screening assessments have been performed within 3 days prior to C1D1, then assessments do not need to be performed on C1D1 pre-dose.

[b] If toxicity of ≥ Grade 3 is observed during Cycles 1 and/or 2, patients should return for additional visits on Day 15 of subsequent cycles to ensure appropriate safety follow-up, per investigator judgement, of the events observed in previous cycles.

[c] If clinically indicated, blood pressure to be measured in the supine and standing positions after at least 10 minutes' rest.

[d] Haematology and clinical chemistry assessments will take place on Day 22 (± 1 day window) of Cycles 1 and 2. If toxicity is detected during these additional safety assessments, the patient will be managed as per the protocol, and as clinically indicated. In the event that a patient has an event of thrombocytopenia, anaemia and/or neutropenia that is ≥ Grade 3 during the first 2 cycles, this additional safety assessment will be included in subsequent cycles until there is no evidence of ≥ Grade 3 thrombocytopenia, anaemia and/or neutropenia for at least 2 cycles.

[e] Patients who develop an event ≥ Grade 3 of thrombocytopenia, anaemia and/or neutropenia later in their treatment will also need to have this additional assessment until there is no evidence of ≥ Grade 3 thrombocytopenia, anaemia and/or neutropenia for at least 2 cycles.

[f] Patients must receive AZD6738 for 14 days within a 28-day durvalumab cycle. A durvalumab cycle must not be < 28 days. AZD6738, once started, must not be given on any other days of the cycle, unless permitted as per the dose modification and discontinuation criteria detailed in Section 6.6, and dosing days must stay relative to the durvalumab administration on Day 1 of each cycle, unless or until durvalumab is permanently stopped, in which case dosing days remain Day 15 to Day 28 of each 4-week cycle. In case of AZD6738 interruption within the planned Day 15 to 28 dosing window (for any reason), resumption of treatment can only take place within the planned dosing window and not beyond, even if this means the subject receives less than the specified 14 days AZD6738 dosing in the particular cycle. In case AZD6738 cannot be started on day 15 of the ongoing cycle, a maximum delay of 28 days is allowed.

[g] Ad hoc collection of survival status may be requested for overall survival analyses.

[h] Following the final data cut-off for the module CSR (see Section 9.4.2 of the core protocol), any patients on study treatment may continue on treatment and should be assessed for safety according to standard local clinical practice. Study drug administration, SAE reporting and related safety assessment data should be recorded in the eCRF until 90 days after study drug discontinuation, when the patient will end participation in the study. The other assessments for the study will no longer be performed and those data will no longer be collected; the tumour evaluations will be performed as per standard of care. The survival follow-up will no longer be conducted.

[i] Whole blood to be taken every cycle for the first 3 cycles and at every radiographic assessment visit (every 6 weeks [± 1 week] for the first 24 weeks relative to the start of therapy (C1D1), then every 8 weeks [±1 week]) in all patients (at pre-dose on durvalumab dosing day) until disease progression (or study treatment discontinuation).

[j] On-treatment biopsy is not required if a fresh tumour sample is not collected at pre-screening.

ADA, Anti-drug antibodies; AE, adverse event; APTT, activated partial thromboplastin time; C, cycle; CD8+, cytotoxic T-cell; CSP, clinical study protocol; CSR, clinical study report; CT, computed tomography; CCI D, day; ECG, electrocardiogram; eCRF, electronic Case Report Form; INR, international normalised ratio; MRI, magnetic resonance imaging; PBMC, peripheral blood mononuclear cell; PD-1, programmed cell death-1; Q12W, every 12 weeks; Q24W, every 24 weeks; RECIST 1.1, Response Evaluation Criteria in Solid Tumours 1.1; SAE, serious adverse event; TCR, T-cell receptor repertoire; TSH, thyroid-stimulating hormone; T_3, triiodothyronine; T_4, thyroxine.

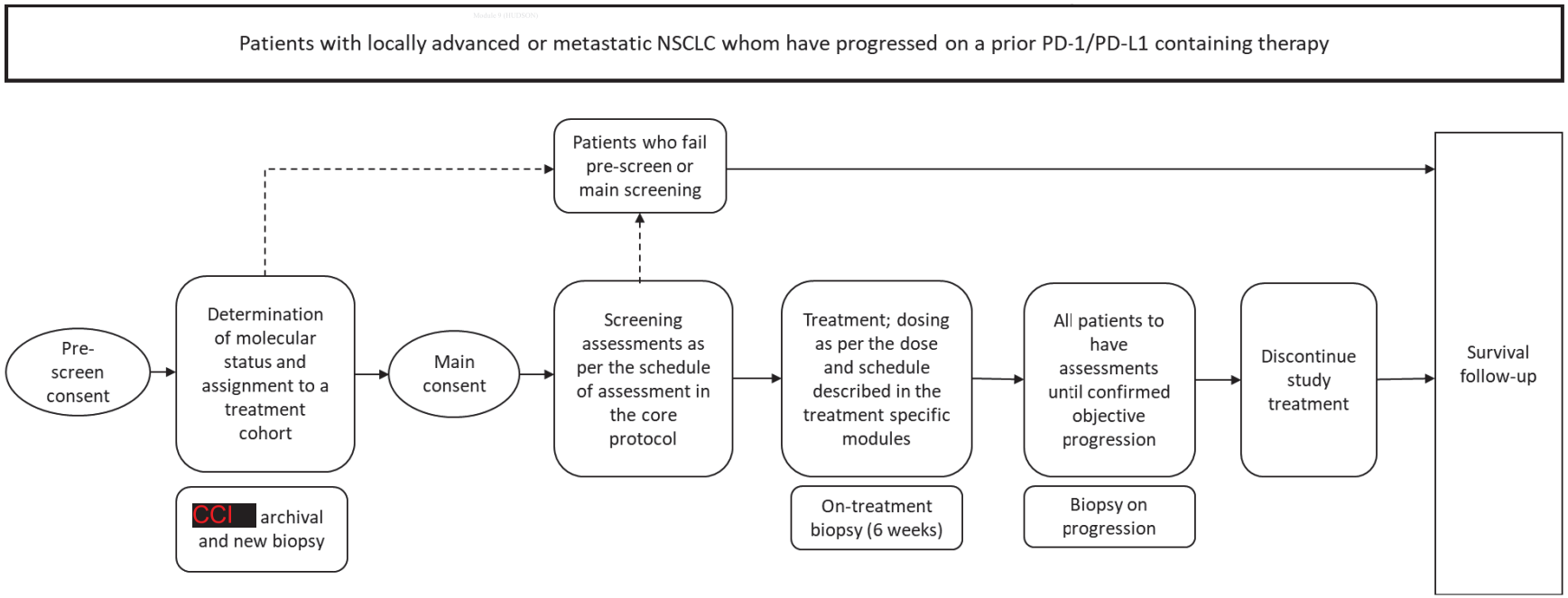
1.2 Synopsis

Please refer to Section 1.2 of the core protocol.

1.3 Schema

The general study design is summarised in Figure 1.

Figure 1 Study Design



Note, as of implementation of protocol v10.0, survival follow-up of screen failures is no longer applicable.
CCI NSCLC, non-small cell lung cancer; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1.

2. INTRODUCTION

Study D6185C00001 (HUDSON) is a Phase II, open-label, multi-centre umbrella study in patients who have received an anti-programmed cell death-1 (PD-1)/anti-programmed cell death-ligand 1 (PD-L1) containing therapy and a platinum-doublet regimen for locally advanced or metastatic non-small cell lung cancer (NSCLC) either separately or in combination. The patient must have had disease progression on a prior line of anti-PD-1/PD-L1 therapy. The modular design allows the evaluation of the efficacy, safety, and tolerability of multiple study drugs. This module to the core study protocol describes Module 9, which will investigate the efficacy, safety, and tolerability of durvalumab administered in combination with AZD6738 (AZD6738 dosed for 14 days [from Days 15 to 28] in every 4-week combination cycle). As of implementation of protocol version 10.0, Module 9 is closed to patient recruitment.

2.1 Study Rationale

As described in Section 2.2 of the core protocol, immune checkpoint inhibitors targeting the PD-1/PD-L1 pathway have shown significant activity in the first- and second-line treatment settings in patients with NSCLC. However, it is becoming evident that there is a new and significant patient population emerging that does not respond to anti-PD-1/PD-L1 containing therapy (primary resistance) or progresses during anti-PD-1/PD-L1 containing therapy (acquired resistance). There is currently no established therapy for patients who have developed resistance to PD-1/PD-L1 and platinum-doublet therapies, and novel treatments for these patients are urgently needed.

The aim of this umbrella study (D6185C00001) is to investigate multiple study drugs for the treatment of NSCLC in molecularly matched and non-matched patient populations after failure of immune checkpoint inhibitors, to identify patient populations who may respond favourably to novel anti-tumour therapies.

2.2 Background

Durvalumab and AZD6738 are both currently in clinical development as anti-cancer therapies in a variety of malignancies.

Durvalumab as a weight-based regimen of 10 mg/kg every 2 weeks (Q2W) has been approved for use in the treatment of patients with urothelial carcinoma (UC). On 16 February 2018, durvalumab was approved in the US for the treatment of patients with unresectable Stage III NSCLC. On 21 September 2018, durvalumab was approved in the European Union (EU) for the treatment of locally advanced, unresectable NSCLC in adults whose tumours express PD-L1 on ≥ 1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy. As of 12 July 2019, durvalumab is approved in over

45 countries for NSCLC. On 27 March 2020, the Food and Drug Administration approved durvalumab in combination with etoposide and either carboplatin or cisplatin as first-line treatment of patients with extensive-stage small cell lung cancer.

Module 9 will investigate both agents in combination (AZD6738 dosed for 14 days [from Days 15 to 28] in every 4-week combination cycle), to test the hypothesis that the combination is feasible and can result in complementary anti-tumour activity at this modified dose and schedule. Brief background on AZD6738 and durvalumab, including their mechanisms of action, is provided below. For detailed descriptions of the chemistry, pharmacology, efficacy, and safety of AZD6738 and durvalumab, refer to the respective Investigator's Brochures (IBs).

The module will recruit biomarker non-matched patients (see Section 4.1).

2.2.1 Durvalumab

2.2.1.1 Overview of Durvalumab

Expression of PD-L1 protein is an adaptive immune response that helps tumours evade detection and elimination by the immune system. PD-L1 can be induced by inflammatory signals (eg, interferon-gamma) and can be expressed on both tumour cells and tumour-associated immune cells in tumour microenvironment. PD-L1 blocks T-cell function and activation through interaction with PD-1 and cluster of differentiation (CD)80 (B7.1). By binding to its receptors, PD-L1 reduces cytotoxic T-cell activity, proliferation, and cytokine production. Durvalumab is a fully human, high affinity, immunoglobulin G1 kappa monoclonal antibody that selectively blocks the interaction of PD-L1 with PD-1 and CD80 (B7.1) while leaving PD-1/programmed cell death ligand-2 interaction intact. Durvalumab does not induce antibody dependent cell-mediated cytotoxicity. Selective blockade of PD-L1/PD-1 and PD-L1/CD80 interactions enhances antitumour immune responses. These antitumour responses may result in tumour elimination.

Durvalumab is approved in a number of territories including the US, EU, Japan, Canada and Brazil under the brand name IMFINZI™ Injection.

The recommended dose as per the IMFINZI package insert is 10 mg/kg administered as an intravenous (IV) infusion over 60 minutes every 2 weeks (Q2W)

For more information, please refer to the latest version of the durvalumab IB.

2.2.1.2 Durvalumab Data

To date, durvalumab has been given to more than 12000 patients as part of ongoing studies either as monotherapy or in combination with other anticancer agents. Details on the safety profile of durvalumab monotherapy are summarized below. Refer to the current durvalumab

IB for a complete summary of pre-clinical and clinical information including safety, efficacy, and pharmacokinetics (PK).

Clinical activity in locally advanced NSCLC

The efficacy of durvalumab was evaluated in the PACIFIC Study, a randomised, double-blind, placebo-controlled, multicentre study in CCI patients with histologically or cytologically confirmed locally advanced, unresectable NSCLC. Patients had completed definitive platinum-based chemoradiation within 1 to 42 days prior to initiation of the study and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Ninety-three percent of patients had received a total dose of 54 to 66 Gy of radiation. The study excluded patients who had progressed following concurrent chemoradiation therapy, patients with active or prior documented autoimmune disease within 2 years of initiation of the study; a history of immunodeficiency; a history of severe immune-mediated adverse reactions; medical conditions that required systemic immunosuppression, except physiological dose of systemic corticosteroids; active tuberculosis or hepatitis B or C or HIV infection or patients receiving live attenuated vaccine within 30 days before or after the start of durvalumab. Patients were randomised 2:1 to receive 10 mg/kg durvalumab (n = 476) or 10 mg/kg placebo (n = 237) via IV infusion Q2W for up to 12 months or until unacceptable toxicity or confirmed disease progression. Randomisation was stratified by gender, age (< 65 years vs. ≥ 65 years) and smoking status (smoker vs. nonsmoker). Patients with disease control at 12 months were given the option to be re-treated upon disease progression. Tumour assessments were conducted every 8 weeks for the first 12 months and then every 12 weeks thereafter.

The demographics and baseline disease characteristics were well balanced between study arms. Baseline demographics of the overall study population were as follows: male (70%), age ≥ 65 years (45%), White (69%), Asian (27%), other (4%), current smoker (16%), past-smoker (75%), and never smoker (9%), World Health Organisation (WHO)/ECOG PS 0 (49%), WHO/ECOG PS 1 (50%). Disease characteristics were as follows: Stage IIIA (54%), Stage IIIB (44%), histological subgroups of squamous (47%), non-squamous (53%), PD-L1 expression in tumour cells (TC) ≥ 25% (22%), PD-L1 expression TC < 25% (41%). (PD-L1 status was retrospectively analysed using the Ventana PD-L1 [SP263] Assay in 451 patients with available samples, taken prior to concurrent chemoradiation therapy.)

At the time of the interim progression-free survival (PFS) analysis, the median PFS by blinded independent central review (BICR) was significantly longer with durvalumab treatment (16.8 months) compared with placebo (5.6 months); hazard ratio 0.52; 98.9% CI: 0.39, 0.70; $p < 0.0001$. At the time of the interim overall survival (OS) analysis, the median OS was not reached for the durvalumab arm and was 29.1 months for the placebo arm; hazard ratio, 0.69; 95% CI, 0.55, 0.86. The 36-month OS rate was 57.0% with durvalumab vs 43.5% with placebo.

Clinical activity in recurrent and metastatic NSCLC

Based on current data from the ongoing Study CD ON MEDI4736-1108 (NCT01693562), evidence of clinical activity with durvalumab has been observed. The following responses were observed in patients with NSCLC.

Overall, clinical activity was observed in both the PD-L1 high (defined as having TC ≥ 25%) and PD-L1 low/negative (defined as TC < 25%) subgroups, however, patients with PD-L1 high tumours had higher objective response rates (ORRs).

The ORR per BICR was 21.8% and 6.4% in patients with PD-L1 high and low/negative tumours, respectively and 15.3% in the overall population regardless of PD-L1 expression. The ORR was 25.9%, 14.3% and 11.5% in the 1L, 2L and 3L+ cohorts, respectively. Median duration of response (DoR) was 17.74 months. Median OS was 12.4 months; median OS was 21.0, 11.8 and 9.3 months in the 1L, 2L and 3L+ cohorts, respectively. The OS rate at 24 months was 29.6%.

The ATLANTIC study in third-line or higher NSCLC showed higher ORR and survival outcomes in high PD-L1 positive patients. Across cohorts the ORR ranged from 3% to 43%, median PFS ranged from 1.8 to 5.5 months and median OS ranged from 5.9 to 13.6 months but was not reached at the time of initial reporting in the > 90% PD-L1 expressors. The ORR and survival outcomes reported in durvalumab studies are in keeping with other similar agents targeting the PD-1/PD-L1 axis (Garassino et al 2017).

Preliminary efficacy data from the MYSTIC study in first-line advanced or metastatic NSCLC showed that in PD-L1 high (≥ 25% TC) NSCLC, median PFS by BICR was 4.7 months for durvalumab monotherapy and 5.4 months for chemotherapy; hazard ratio of 0.87; 99.5% CI: 0.593, 1.285; p = 0.324. The median OS was 16.3 months for the durvalumab arm and 12.9 months for the chemotherapy arm; hazard ratio for death was 0.76; 97.54% CI: 0.564, 1.019; p = 0.036. The 24-month OS rate was 38.3% vs 22.7% and the 12-month PFS rate was 32.3% vs 14.3% for the durvalumab and chemotherapy arms respectively. When durvalumab was administered in combination with tremelimumab, the median PFS by BICR was 3.9 months for durvalumab + tremelimumab and 5.4 months for chemotherapy; hazard ratio of 1.05; 99.5% CI: 0.722, 1.534; p = 0.705. The median OS was 11.9 months for the durvalumab + tremelimumab arm and 12.9 months for the chemotherapy arm; hazard ratio for death was 0.85; 98.77% CI: 0.611, 1.173; p = 0.202. The 24-month OS rate was 35.4% vs 22.7% and the 12-month PFS rate was 25.8% vs 14.3% for the durvalumab + tremelimumab and chemotherapy arms respectively.

Immuno-oncology agents targeting the PD-1/PD-L1 pathway have demonstrated activity as monotherapy and in combination with chemotherapy in patients who are immunotherapy-naïve. However, the present study will recruit patients who either have primary resistance to

anti-PD-1/PD-L1 therapy or who developed acquired resistance while on anti-PD-1/PD-L1 therapy. Thus, in this immunotherapy-resistant setting, durvalumab will be administered in combination with an agent that has a different and complementary mechanism of action in order to maximise the likelihood of clinical activity.

2.2.2 AZD6738

2.2.2.1 Overview of AZD6738

AZD6738 is a potent, selective inhibitor of ataxia telangiectasia and Rad3-related protein (ATR), with good selectivity against other phosphatidylinositol 3-kinase-related kinase (PIKK) family members. This compound is being developed as an oral anti-tumour agent in patients with disease that is dependent upon ATR function for DNA repair; an example being tumours that are deficient of the serine/threonine specific protein kinase, ataxia telangiectasia mutated (ATM).

ATR is a serine/threonine protein kinase and member of the PIKK family. During normal DNA replication, ATR is activated by persistent single strand DNA breaks (SSBs) that occur if a replication fork is stalled in S-phase during DNA synthesis. Activation of ATR triggers a signal cascade leading to cell cycle arrest in S-phase whilst the DNA is repaired and the stalled replication fork resolved. Without repair, SSBs can progress to double strand DNA breaks (DSBs), the most genotoxic form of DNA damage due to the consequences DSBs have for accurate chromosome segregation during cell division (O'Connor 2015). ATR is also recruited to single-strand DNA coated with Replication Protein A following single strand DNA damage or the resection of DSBs.

AZD6738 is an inhibitor of ATR that blocks this activity, causing stalled replication forks to collapse leading to DSBs and a dependence on ATM, a key enzyme coordinating the cellular response to DSBs (Weber and Ryan 2015). If the level of DNA damage exceeds the capacity to repair, nuclear fragmentation and entry into programmed cell death (apoptosis) occur (Cimprich and Cortez 2008).

ATM is a closely related kinase that is recruited to DSBs and like ATR, has both checkpoint and repair functions. In normal cells, there is a significant interplay between ATR and ATM as stalled replication forks can be converted into DSBs through further DNA damage and the resection of DSBs generates single-strand DNA (Stewart et al 2015; Toledo et al 2011). Sporadic ATM deficiency is reported in many tumour types, and ATM deficiency is expected to sensitise tumour cells to ATR inhibition through their complementary roles in DNA damage repair. Patients with ATM-deficient malignancies can be clinically identified and, in most cases, are known to have a poor prognosis with current therapies. ATM expression is commonly lost/reduced in NSCLC (Villaruz et al 2016).

2.2.2.2 AZD6738 Clinical Programme

Currently, for the ATR programme, there are a number of ongoing AstraZeneca sponsored clinical studies with AZD6738 in addition to HUDSON, where combinations of AZD6738 with carboplatin, olaparib or durvalumab are being explored.

There are 3 other AstraZeneca sponsored studies incorporating AZD6738 in combination with olaparib:

D419QC00002 (BALTIC, NCT02937818) using AZD6738 and olaparib combination in patients with platinum refractory extensive-stage small-cell lung cancer, has completed with 21 patients dosed. D5336C00001 (VIOLETTE, NCT03330847) using the AZD6738 and olaparib combination in patients with triple negative breast cancer with BRCA mutation (stratum A), HRR mutation (stratum B) and non-HRR mutation (stratum C), was closed based on primary analysis CCI Based on primary analysis in stratum A of the D5336C00001 study, D6018C00004 (DUETTE, NCT04239014) using the combination of AZD6738 and olaparib as second maintenance treatment in patients with platinum-sensitive relapsed epithelial ovarian cancer, who have previously received PARP inhibitor maintenance treatment, was terminated (no patients were randomised to treatment).

A previous Phase I study (D5330C00001; NCT01955668) to assess multiple ascending doses of AZD6738 in patients with prospectively identified 11q-deleted relapsed/refractory chronic lymphocytic leukaemia (CLL), prolymphocytic leukaemia or B cell lymphomas was stopped CCI patient was treated, due to difficulties in recruitment. An AstraZeneca sponsored study (D5330C00008, NCT03328273) is testing AZD6738 combination with acalabrutinib in patients with relapsed/refractory CLL; the monotherapy part of the study has been stopped due to difficulties in recruiting the required patient population.

In addition, there are Externally Sponsored Research (ESR) studies ongoing where AZD6738 is being investigated as a single agent or in combination with radiotherapy (PATRIOT study [D5330C00002; NCT02223923]; recruitment complete), in combination with paclitaxel or durvalumab (Pre-VIKTORY study [D5330C00006; NCT02630199] in patients with advanced solid tumors and enriched with metastatic melanoma and VIKTORY study [D6183C00003; NCT02299648] in patients with metastatic melanoma and gastric cancer; recruitment complete in both studies), or in combination with olaparib in ovarian carcinoma (CAPRI study [D5334C00001; NCT03462342]) and in patients with solid tumours harbouring mutations in homology-directed repair genes (OLAPCO [D0810C00090; NCT02576444]; recruitment complete), in patients with relapsed small cell lung cancer (SUKES-N2 [D5334C00003; NCT03428607]; recruitment complete), in triple negative breast cancer (PlasmaMATCH Cohort E [D6184C00001; NCT03182634]; recruitment complete), and in BAF250a (ARID1A)-deficient or BAF250a-expressing advanced solid cancers (D5330C00012; NCT03682289).

See the current Investigator's Brochure for further information.

2.2.3 Durvalumab and AZD6738 in Combination

The underpinning hypothesis for combining durvalumab and AZD6738 is that the combination will result in induction of immune memory, leading to more durable control of tumour growth than is achievable with either modality alone. Molecularly targeted therapies may serve as "cancer vaccines" inducing the killing of tumour cells and resulting in the release of tumour antigens and neoantigens, which can then be presented by antigen presenting cells (APCs) to tumour-specific T-cells. These T-cells become activated but also upregulate inhibitory checkpoints such as CTLA-4 and PD-1, which can be blocked with antibodies to permit enhanced anti-tumour T-cell responses, including memory T-cell responses, to enable long-term control of disease and possible cure. In addition, the use of targeted agents to directly kill tumour cells, with release of tumour antigens, may focus the activated immune response generated by immunotherapy agents on tumour antigens rather than self-antigens expressed on normal tissues, resulting in fewer adverse events (AEs).

Based on our current understanding of the immune response, one can identify 3 distinct steps that must be achieved in order to mount effective anti-tumour immunity (Mellman et al 2011):

1 To initiate immunity, dendritic cells must sample antigens derived from the tumour, mature and differentiate, and ultimately process and present tumour antigens
2 Next, in lymphoid organs, tumour antigen-loaded dendritic cells must generate protective T-cell responses
3 Finally, cancer specific T-cells must enter the tumour bed to perform their function. To do so, they have to overcome the challenge of stromal immune suppression.

Single agent PD-1/PD-L1 axis inhibitors primarily impact this third step: relieving stromal suppression. ATR inhibition causes an increase in S-phase DNA damage in tumour cells that is expected to lead to the accumulation of unincorporated DNA fragments in the cytosol, activating the stimulator of interferon genes (STING)/tank binding kinase-1 (TBK1)/interferon regulatory factor-3 (IRF3) innate immune response (Parkes et al 2017). If sufficient DNA damage accumulates, tumour cell death is expected to release tumour specific antigens, changing the tumour microenvironment to promoting antigen presentation (Galluzzi et al 2012). Either consequence of ATR inhibition has the potential to prime the immune response, as outlined in Step 1 above.

It is expected that if loss of PD-L1 expression is involved in generation of resistance to front-line PD-1/PD-L1 axis inhibitors that the combination of durvalumab with AZD6738, by removing the dependence on PD-L1 expression, will restore sensitivity.

The combination of durvalumab and AZD6738 has been investigated in AstraZeneca Study D5530C00004 (Module 3), at the following dose regimens:

- Cohort 1 AZD6738 80 mg twice daily (bd) Cycle 0 Days 1 to 14, Cycle 1 Days 22 to 28
- Cohort 2 AZD6738 160 mg bd Cycle 0 Days 1 to 14, Cycle 1 Days 22 to 28
- Cohort 3 AZD6738 320 mg once daily (od) Cycle 0 Days 1 to 14, Cycle 1 Days 22 to 28
- Cohort 4 AZD6738 320 mg od Cycle 0 Days 1 to 14, Cycle 1 Days 15 to 28
- Cohort 5 AZD6738 240 mg bd Cycle 0 Days 1 to 7, Cycle 1 Days 22 to 28
- Cohort 6 AZD6738 240 mg bd Cycle 0 Days 1 to 14, Cycle 1 Days 15 to 28.

and in AstraZeneca Study HUDSON (Module 3), at the following dose regimen:

- AZD6738 240 mg bd Cycle 0 Days 1 to 7, Cycle 1 Days 22 to 28.

AZD6738 240 mg bd Cycle 0 Days 1 to 14, Cycle 1 Days 15 to 28 combined with durvalumab 1500 mg on day 1 q28 was declared as the recommended Phase II dose.

Clinical experience of the combination of AZD6738 and durvalumab is summarised in the AZD6738 IB; additionally the preliminary results from HUDSON Module 3 are presented in Section 2.2.3.1. A preliminary signal of efficacy has been observed in both AZ sponsored trials in patients with NSCLC and squamous cell carcinoma of the head and neck [SCCHN] and in an ESR (VIKTORY) investigating the combination of AZD6738 240 mg twice daily from Day 15 to 28 every 4 weeks and durvalumab 1500 mg on Day 1 every 4 weeks in patients with gastric cancer and immuno-oncology refractory melanoma. The VIKTORY study has completed recruitment with 61 patients enrolled across both cohorts.

HUDSON Module 9 will investigate whether the combined effects of AZD6738 and durvalumab can overcome the immune-resistance that has been developed clinically in patients treated with prior PD-1/PD-L1 containing therapy, at a different dosing regimen to that tested in HUDSON Module 3. An exposure to AZD6738 of 14 days (Days 15 to 28) per 4-week durvalumab cycle in Module 9 as opposed to 7 days (Days 22 to 28) in Module 3 will ensure that the majority of patients will have AZD6738 exposure above the estimated concentration of an inhibitor where ATR catalytic activity is reduced by 90% (IC_{90}) during the dosing interval; the longer treatment duration is predicted to maintain AZD6738 concentrations above the IC_{90} threshold for 12 hours in 90% of patients (data on file). A 14-day recovery is required to allow platelet recovery and avoid cumulative bone marrow toxicity, particularly thrombocytopenia.

No reproductive toxicology nor teratogenic studies have been conducted with AZD6738 to date, and it is unknown whether the drug is excreted in human milk. Therefore, women of childbearing potential and men should agree to use adequate contraception prior to study entry

and for the duration of study participation, and women who are breast feeding are excluded from the study. Both women and men should be fully informed of the lack of reproductive toxicity testing, and women must have a negative pregnancy test prior to enrolment.

2.2.3.1 Emerging Data from Module 3 of HUDSON

In the current Phase II, open-label, multicentre umbrella study (D6185C00001; HUDSON) the combined effects of AZD6738 and durvalumab in overcoming immune-resistance in patients who failed PD-1/PD-L1 containing therapy are being investigated. The efficacy, safety, and tolerability of durvalumab administered in combination with AZD6738 has been investigated in both biomarker-matched (A.3.ATM) and biomarker non-matched (B.3.PRI and B.3.ACQ) patients (Module 3). Following a 1-week AZD6738 monotherapy dosing, AZD6738 is being dosed for 7 days (Days 22 to 28) out of every 4-week durvalumab cycle.

As of 26 January 2021, C patients have been dosed in Module 3 (C A.3.ATM, C B.3.PRI and C B.3.ACQ). Cohorts B.3.PRI and B.3.ACQ are closed for enrolment as the required number of patients per cohort has been reached. As per the data cut-off date (26 January 2021), all C dosed patients dosed patients were evaluable for response, with CCI patients still on study treatment. The ORR across Module 3 was CCI In the B.3.PRI cohort, the ORR was CCI confirmed PRs) with a DCR of CCI at C weeks. In the B.3.ACQ cohort, the ORR was CCI confirmed PRs) with a DCR of 32% at 24 weeks. Landmark 6, 9 and 12 months PFS and OS data are promising across all cohorts (although the C months OS data is CCI for the A.3.ATM cohort). At the time of preparation of CSP version 8.1, Module 3 is ongoing and therefore data will be subject to change.

The safety profile of durvalumab and AZD6738 combination in HUDSON has been CCI with other ongoing studies. Of the C patients with safety data available, the most frequent (≥ 15%) AEs were reported as: CCI The most frequent (≥ 5%) CTCAE Grade ≥ 3 AEs were reported as: CCI The most commonly reported SAE across the durvalumab/AZD6738 combination was CCI patients. The majority of SAEs reported were confounded by risk factors other than study therapy such as medical history, concurrent conditions and concomitant medications. Overall, CCI patients discontinued treatment with AZD6738 due to AEs, and CCI of these patients also discontinued durvalumab. The overall safety was CCI At the time of preparation of CSP version 8.1, Module 3 is ongoing and therefore data will be subject to change. For the most up-to-date information, please see the AZD6738 IB.

Anaemia, thrombocytopenia, and neutropenia (including febrile neutropenia), CCI [redacted] have been reported when AZD6738 is used as monotherapy and when used in combination with durvalumab.

The AEs reported for AZD6738 + durvalumab are CCI [redacted] with those reported for AZD6738 in combination with either carboplatin and olaparib, were predictable from non-clinical data and from what is known about the mechanism of action of AZD6738, durvalumab and/or the underlying disease. The observed toxicities in the clinical CCI [redacted] with current clinical practice. See the IB for further information. At the time of preparation of CSP version 8.0, Module 3 is ongoing and therefore data will be subject to change.

2.3 Benefit/risk Assessment

As described in Section 2.3 of the core protocol, patients recruited to this study are not expected to have other treatment options apart from monotherapy chemotherapy, such as docetaxel. The survival outcome and toxicity profile of chemotherapy in this setting mean that other active therapies are highly desirable and present a potential advantage for patients.

The study design aims to identify patient populations who may respond favourably to novel anti-tumour therapies. Based upon the available non-clinical and clinical safety data, the limited survival benefit provided by the currently available treatment options to patients, the limited life expectancy due to malignant disease, and the hypothesis of the complementary effect of the 2 agents, the investigation of the potential therapeutic efficacy of the combination of durvalumab with AZD6738, at this modified dose and schedule, in patients with advanced or metastatic NSCLC is acceptable, and the overall benefit/risk assessment supports the proposed study design.

3. OBJECTIVES AND ENDPOINTS

Please refer to the core protocol.

4. STUDY DESIGN

4.1 Overall Design

This is an open-label, multi-centre, umbrella study in patients who have received an anti-PD-1/PD-L1 containing therapy and a platinum-doublet regimen for locally advanced or metastatic NSCLC either separately or in combination. The patient must have had disease progression on a prior line of anti-PD-1/PD-L1 therapy. For an overview of the study design see Figure 1; further details on the overall design are provided in Section 4 of the core protocol. For details on the study treatments given in Module 9, see Section 6.1.

Module 9 will evaluate the efficacy, safety, and tolerability of durvalumab (given IV) in combination with AZD6738 (given orally from Day 15 to Day 28 of each durvalumab cycle) in 2 cohorts of biomarker non-matched patients as follows:

- **Cohorts B.9** will investigate the efficacy, safety, and tolerability of durvalumab (given IV) in combination with AZD6738 (given orally) in patients stratified by prior response to immunotherapy; primary resistance (Cohort B.9.PRI) or acquired resistance (Cohort B.9.ACQ). These terms are defined as follows:
  - Primary resistance; patients who had anti-PD-1/PD-L1 containing therapy but had progression of disease (PD) within ≤ 24 weeks from the start of treatment.
  - Acquired resistance; patients who had progressive disease > 24 weeks from the start of anti-PD-1/PD-L1 containing therapy whilst still on that treatment.

As of implementation of protocol version 10.0, patient recruitment to Module 9 is closed (refer to Section 4.1 of the core protocol for details).

A study flow diagram is provided in the core protocol (Figure 4).

A comprehensive review of all safety data will be conducted in approximately the first 6 patients; these patients will be followed for 1 cycle to ensure the treatment schedule is safe and tolerable. The study procedures and safety assessments undertaken for the first cycle will be as per the SoA (Table 1). Recruitment will continue whilst the safety review is performed. The safety assessment will be undertaken by a Safety Review Committee (SRC). The role and responsibilities of SRC members, as well as the purpose and timing of the SRC meetings are described in the SRC Charter (core protocol Appendix A).

4.2 Scientific Rationale for Study Design

The study aims to identify patient populations who may respond favourably to novel anti-tumour therapies, and the modular design allows evaluation of the efficacy, safety, and tolerability of multiple study drugs. The study requires an open-label design owing to the different schedules and routes of administration of the study drugs.

Module 9 will include biomarker non-matched cohorts B.9.PRI (primary resistant) and B.9.ACQ (acquired resistant). The proliferative drive and genomic instability of cancer cells leads to high background levels of DNA damage and repair. Increasing the levels of S-phase DNA damage by ATR inhibition is expected to lead to the accumulation of unincorporated DNA fragments in the cytosol, activating the STING/TBK1/IRF3 innate immune response, and reversing resistance to immunotherapy (Parkes et al 2017). Checkpoint blockade at the same time by durvalumab is expected to overcome the inhibitory action of PD-L1 on T-cell activation.

4.3 Justification for Dose

4.3.1 Justification for Durvalumab Dose

A durvalumab dose of 20 mg/kg Q4W is supported by in vitro data, pre-clinical activity, clinical PK/pharmacodynamics, biomarkers, and activity data from Study CD-ON-MEDI4736-1108 (hereafter referred to as Study 1108) in patients with advanced solid tumors and from a Phase I study performed in Japanese patients with advanced solid tumor (D4190C00002).

PK/Pharmacodynamic data

Based on available PK/pharmacodynamic data from ongoing Study 1108 with doses ranging from 0.1 to 10 mg/kg Q4W or 15 mg/kg Q4W, durvalumab exhibited non-linear (dose dependent) PK consistent with target-mediated drug disposition. The PK approached linearity at ≥ 3 mg/kg Q4W, suggesting near complete target saturation (membrane-bound and sPD-L1), and further shows that the durvalumab dosing frequency can be adapted to a particular regimen given the linearity seen at doses higher than 3 mg/kg. The expected half-life with doses ≥ 3 mg/kg Q4W is approximately 21 days. A dose-dependent suppression in peripheral sPD-L1 was observed over the dose range studied, consistent with engagement of durvalumab with PD-L1. A low level of immunogenicity has been observed. No patients have experienced immune-complex disease following exposure to durvalumab. (For further information on immunogenicity, please see the current durvalumab IB.)

A population PK model was developed using the data from Study 1108 (doses = 0.1 to 10 mg/kg Q2W or 15 mg/kg Q4W; Fairman et al 2014). Multiple simulations indicate that a similar overall exposure is expected following both 10 mg/kg Q4W and 20 mg/kg Q4W regimens, as represented by area under the plasma concentration-time curve at steady state (AUC_{ss}) (4 weeks). Median maximum plasma concentration at steady state ($C_{max,ss}$) is expected to be higher with 20 mg/kg Q4W (~1.5-fold) and median trough plasma concentration at steady state ($C_{trough,ss}$) is expected to be higher with 10 mg/kg Q4W (~1.25-fold). Clinical activity with the 20 mg/kg Q4W dosing regimen is anticipated to be consistent with 10 mg/kg Q4W with the proposed similar dose of 20 mg/kg Q4W expected to (a) achieve complete target saturation in majority of patients; (b) account for anticipated variability in PK, pharmacodynamics, and clinical activity in diverse cancer populations; (c) maintain sufficient PK exposure in case of anti-drug antibody impact; and (d) achieve PK exposure that yielded maximal antitumor activity in animal models.

Given the similar area under the serum drug concentration-time curve (AUC) and modest differences in median peak and trough levels at steady state, the observation that both regimens maintain complete sPD-L1 suppression at trough, and the available clinical data, the 20 mg/kg Q4W and 10 mg/kg Q4W regimens are expected to have similar efficacy and safety profiles, supporting further development with a dose of 20 mg/kg Q4W.

Clinical data

Refer to the current durvalumab IB for a complete summary of clinical information including safety, efficacy, and PK at the 20 mg/kg Q4W regimen.

Rationale for fixed dosing

A population PK model was developed for durvalumab using monotherapy data Study 1108 (N = 292; doses = 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W; solid tumors). Population PK analysis indicated only minor impact of body weight on the PK of durvalumab (coefficient of ≤ 0.5). The impact of body weight-based (10 mg/kg Q2W) and fixed dosing (750 mg Q2W) of durvalumab was evaluated by comparing predicted steady state PK concentrations (5th, median, and 95th percentiles) using the population PK model. A fixed dose of 750 mg was selected to approximate 10 mg/kg (based on median body weight of ~75 kg). A total of 1000 patients were simulated using body weight distribution of 40 to 120 kg. Simulation results demonstrate that body weight-based and fixed dosing regimens yield similar median steady state PK concentrations with slightly less overall between-patient variability with fixed dosing regimen.

Similar findings have been reported by others (Narwal et al 2013, Ng et al 2006, Wang et al 2009, Zhang et al 2012). Wang and colleagues investigated 12 monoclonal antibodies and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies (Wang et al 2009). In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-patient variability in PK/pharmacodynamic parameters (Zhang et al 2012).

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar PK exposure and variability, AstraZeneca considered it feasible to switch to fixed dosing regimens. Based on average body weight of 75 kg, a fixed dose of 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) is included in the current study.

An exception to 1500 mg fixed dosing is made for patients with low body weight (below 30 kg). Patients with a body weight of 30 kg or less must receive weight-based dosing, equivalent to 20 mg/kg, until weight increases to greater than 30 kg. At this time, fixed dosing data for patients weighing below 30 kg (corresponding to doses greater than 50 mg/kg) are not available and are not yet supported by product development.

Thus, the clinical activity observed coupled with the safety profile, translational science correlates, and non-clinical data supports further development with a dose of 1500 mg Q4W. The durvalumab dose will not be modified during the study.

4.3.2 Justification for AZD6738 Dose

The dose of AZD6738 for this module is 240 mg twice daily from Day 15 to Day 28 of every 28-day cycle. This dose has been used in combination with durvalumab 1500 mg administered on Day 1 of each 28-day cycle in Study D5330C00004 (NCT02264678) where 30 patients with NSCLC and HNSCC have been treated (data cut-off 13 June 2021); AZD6738 240 mg twice daily was given as monotherapy in Cycle 0 for C days (Days C to C) and then from Day C to Day C in each subsequent cycle in combination with durvalumab. Based on this study, AZD6738 240 mg bd from Day C to Day C of every 28-day cycle in combination with durvalumab 1500 mg Day 1 of each 28-day cycle, was declared as the recommended Phase II dose.

AZD6738 240 mg twice daily from Day 15 to Day 28 of every 28-day cycle in combination with durvalumab 1500 mg administered on Day 1 of each 28-day cycle is also used in an ongoing ESR study in South Korea in patients with malignant melanoma and metastatic gastric cancer (VIKTORY; NCT02630199). The VIKTORY study has completed recruitment with C patients enrolled across both cohorts (C melanoma patients and C gastric cancer patients). As of a data cut-off of 30 June 2020, CCI patients and CCI patients had experienced Grade ≥ 3 AEs; the most frequently reported of these were CCI in the gastric cancer cohort and CCI in the melanoma cohort) and CCI in the gastric cancer cohort and C patients CCI in the melanoma cohort). CCI of the C patients CCI experienced SAEs; C of these events CCI

The dose level of 240 mg twice daily is predicted to maintain AZD6738 concentrations above the estimated IC_{90} threshold for C hours in CCI of patients (data on file). A sigmoid model links AZD6738 exposure with the difference between CCI (pharmacodynamic modulation) and CCI (the main CCI of AZD6738).

Based on the aforementioned data, the use of AZD6738 240 mg twice daily from Day C to Day C of every C -day cycle in combination with durvalumab in this module is justified. Furthermore, considering emerging PK data from the ongoing study (D5330C00004, NCT02264678), CCI

4.4 End of Study Definition

Please refer to the core protocol.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study in order to be assigned to a study cohort. Under no circumstances can there be exceptions to this rule. Patients who do not meet the entry requirements are screen failures; refer to Section 5.4 of the core protocol.

5.1 Inclusion Criteria (Module 9-specific)

Patients are eligible to be included in the study only if all the following inclusion criteria apply. Please also refer to the Section 5.1 of the core protocol for the inclusion criteria applicable to all modules in the study. Additional inclusion criteria applicable to Module 9 only are described in this section.

Q-1 Patients must fulfil all the core eligibility criteria.

5.2 Exclusion Criteria (Module 9-specific)

Patients must not enter Module 9 if any of the following exclusion criteria apply. Refer to Section 5.2 of the core protocol for the exclusion criteria applicable to all modules in the study. Additional exclusion criteria applicable to Module 9 only are described below:

Medical conditions

Q-1 Diagnosis of ataxia telangiectasia.

Q-2 Refractory nausea and vomiting, chronic gastrointestinal diseases or previous significant bowel resection, with clinically significant sequelae that would preclude adequate absorption of AZD6738.

Q-3 Inadequate bone marrow reserve or organ function as demonstrated by any of the following laboratory values: absolute neutrophil count (ANC) $< 1.5 \times 10^9$/L; platelet count $< 100 \times 10^9$/L; haemoglobin < 90 g/L.

Q-4 Persisting (> 4 weeks) severe pancytopenia due to previous therapy rather than disease (ANC $< 0.5 \times 10^9$/L or platelets $< 50 \times 10^9$/L).

Q-5 Creatinine clearance < 45 mL/min calculated by Cockcroft-Gault equation (see Table 5 in the core protocol for the calculation).

Q-6 Haematuria: +++ on microscopy or dipstick.

Q-7 International normalised ratio (INR) ≥ 1.5 or other evidence of impaired hepatic synthesis function.

Q-8 Alkaline phosphatase (ALP) > 2.5 × upper limit of normal (ULN) (and liver disease unrelated to the tumour). Patients with elevated ALP due to tumour related bone metastases or liver metastases will be eligible.

Q-9 Patients with relative hypotension (< 100/60 mmHg) or clinically relevant orthostatic hypotension, including a fall in blood pressure of > 20 mmHg.

Prior/concomitant therapy

Q-10 Receiving, or having received, concomitant medications, herbal supplements and/or foods that significantly modulate cytochrome P450 3A4 (CYP3A4) or P-glycoprotein (P-gp) activity (washout periods of 2 weeks, but 3 weeks for St. John's Wort). Note these include common azole antifungals, macrolide antibiotics and other medications.

Q-11 Prior exposure to an ATR inhibitor.

Other

Q-12 Inability to swallow the formulated product.

For procedures for withdrawal of incorrectly enrolled patients see Section 7.3 of the core protocol.

5.3 Lifestyle Restrictions

5.3.1 Restrictions Applicable to Durvalumab

Patients should not donate blood or blood components while participating in this study and through 90 days after receipt of the final dose of durvalumab or until alternate anticancer therapy is started.

Immunosuppressive medications including, but not limited to systemic corticosteroids at doses beyond 10 mg/day of prednisone or equivalent, methotrexate, azathioprine and tumour necrosis factor alpha blockers are prohibited. Use of immunosuppressive medications for the management of study drug-related AEs and in patients with contrast allergies is acceptable. In addition, use of topical, inhaled and intranasal corticosteroids is permitted (see Table 3).

Live attenuated vaccines within 30 days of durvalumab dosing are prohibited (ie, 30 days prior to the first dose, during treatment with durvalumab and for 180 days post-discontinuation of durvalumab) (see Table 3). Inactivated viruses, such as those in the influenza vaccine or authorised and approved Coronavirus Disease 2019 (COVID-19) vaccines, are permitted (see Table 4).

5.3.2 Restrictions Applicable to AZD6738

Please refer to Section 5.3 of the core protocol for contraception requirements.

5.4 Screen Failures

Please refer to the core protocol.

6. STUDY TREATMENTS

Study treatment is defined as any study drug(s) (including marketed product comparator and placebo) or medical device(s) intended to be administered to a study participant according to the study protocol. Study treatment in Module 9 refers to durvalumab and AZD6738.

6.1 Treatments Administered

6.1.1 Study Drugs

Table 2 Study Drugs

	AZD6738	Durvalumab
Dosage formulation:	Oral tablets in either 20, 80 or 100 mg	Supplied as a vialed liquid solution containing 500 mg (nominal) durvalumab per vial. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine hydrochloride, 275 mM trehalose dihydrate, 0.02% (w/v) polysorbate 80, at pH 6.0. The nominal fill volume is 10.0 mL.
Route of administration:	Oral	IV infusion
Dosing instructions:	240 mg twice daily from Days 15 to 28 in each cycle.	Patients enrolled in the study will receive 1500 mg via IV infusion Q4W ± 2 days (fixed dosing for patients > 30 kg body weight).
Packaging and labelling	Study drug will be provided in high-density polyethylene bottles with child-resistant closures. Labels will be prepared in accordance with GMP and local regulatory guidelines.. Label text will be translated into local language, as required. AZD6738 will be provided with either single-panel labels or multi-language booklet labels. Specific dosing instructions will not be included on the label; the site must complete the "Patient Dispensing Card" with the details of the dosing instructions at the time of dispensing. The Investigator's emergency contact details will not be on the label, but can be found in the informed consent and the 'Patient Dispensing Card'. For emergency purposes the patient must be in possession of the emergency contact details at all times.	Study drug will be provided in vials. Each vial will be labelled in accordance with GMP and per country regulatory requirement. Labels will be prepared in accordance with GMP and local regulatory guidelines. Label text will be translated into local language, as required. Durvalumab will be provided with either single-panel labels or multi-language booklet labels. The Investigator's emergency contact details will not be on the label, but can be found in the informed consent and the 'Patient Emergency Card'. For emergency purposes the patient must be in possession of the emergency contact details at all times.

Table 2 Study Drugs

	AZD6738 (HUDSON)	Durvalumab
Provider	AstraZeneca	AstraZeneca. Commercially available 0.9% (w/v) saline or 5% (w/v) dextrose IV bags will be supplied by each site.

bd, twice daily; GMP, Good Manufacturing Practice; IV, intravenous(ly); Q4W, every 4 weeks; w/v, weight/volume

6.2 Preparation/Handling/Storage/Accountability

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study drugs received and any discrepancies are reported and resolved before use of the study drug.

Only patients enrolled in the study may receive study drugs and only authorised site staff may supply or administer study drugs. All study drugs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorised site staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study drugs accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study drug are provided in the Pharmacy Manual.

6.2.1 Durvalumab Preparation and Handling

Durvalumab will be supplied by AstraZeneca as a 500 mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine hydrochloride, 275 mM trehalose dihydrate, and 0.02% (weight/volume [w/v]) polysorbate 80; it has a pH of 6.0 and a density of 1.054 g/mL. The nominal fill volume is 10.0 mL.

Study drug vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. The vials should be kept in the original packaging until use to prevent prolonged light exposure.

The dose of durvalumab for administration must be prepared by the Investigator's or site's designated study drug manager using aseptic technique. Total time from needle puncture of the durvalumab vial to the start of administration should not exceed 4 hours at room temperature or 24 hours at 2°C to 8°C (36°F to 46°F). If the final product is stored at both refrigerated and ambient temperatures, the total time should not exceed 24 hours.

A dose of 1500 mg (for patients > 30 kg body weight) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab concentration ranging from 1 to 15 mg/mL and delivered through an IV-administration set with a 0.2 μm or

0.22 µm filter. Add 30.0 mL (ie, 1500 mg) of durvalumab to an appropriately sized IV bag such that the final concentration is within 1 to 15 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

If a patient's body weight falls ≤ 30 kg during the study, (s)he will be withdrawn from the study treatment unless (s)he derives some clinical benefit according to the treating physician. In this case, and following agreement between the treating physician and the Sponsor, the patient may continue treatment at a body-weight adapted dose of 20 mg/kg actual body weight.

Weight-based dosing at 20 mg/kg (for patients ≤ 30 kg) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab concentration ranging from 1 to 15 mg/mL, and delivered through an IV administration set with a 0.2 µm or 0.22 µm filter. An example of a weight-based dose calculation is shown in Section 6.2.1.1.

Standard infusion time is one hour (± 15 minutes), however if there are interruptions during infusion, the total allowed infusion time should not exceed 8 hours at room temperature.

If either preparation time or infusion time exceeds the time limits a new dose must be prepared from new vials. Durvalumab does not contain preservatives, and any unused portion must be discarded.

Do not co-administer other drugs through the same infusion line.

The IV line will be flushed with a volume of IV diluent equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered.

Patients will be monitored before, during, and after the first durvalumab infusion with assessment of vital signs at the times specified in the SoA (Table 1) and Section 8.2.3 of the core protocol. If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be at the Investigator's discretion (suggested 30 minutes after each durvalumab infusion). For management of patients who experience an infusion reaction, please refer to the toxicity and management guidelines for infusion-related reactions.

Durvalumab (1500 mg) will be administered via IV infusion Q4W ± 2 days. Treatment with durvalumab will commence on Day 1 following confirmation of eligibility and will continue on a Q4W schedule until disease progression is confirmed.

6.2.1.1 Durvalumab Weight-based Calculation

If a patient's body weight falls ≤ 30 kg during the study, (s)he will be withdrawn from the study treatment unless (s)he derives some clinical benefit according to the treating physician.

In this case, and following agreement between the treating physician and the Sponsor, the patient may continue treatment at a body-weight adapted dose of 20 mg/kg of durvalumab Q4W until the weight improves to > 30 kg, at which point the patient should start receiving the fixed dosing of durvalumab 1500 mg Q4W:

1 Cohort dose: X mg/kg

2 Patient weight: Y kg

3 Dose for patient: XY mg = X (mg/kg) × Y (kg)

4 Dose to be added into infusion bag:

Dose (mL) = XY mg/50 (mg/mL) where 50 mg/mL is durvalumab nominal concentration. The corresponding volume of durvalumab should be rounded to the nearest tenth mL (0.1 mL). Dose adjustments for each cycle are only needed for greater than 10% change in weight.

5 The number of vials required for dose preparation is the next greatest whole number of vials from the following formula:
Number of vials = Dose (mL) / 10.0 (mL/vial)

Example:

1 Cohort dose: 20 mg/kg
   (a) Patient weight: 30 kg
   (b) Dose for patient: 600 mg = 20 (mg/kg) × 30 (kg)
   (c) Dose to be added into infusion bag:
   Dose (mL) = 600 mg / 50 (mg/mL) = 12.0 mL
   (d) The number of vials required for dose preparation:
   Number of vials = 12.0 (mL) / 10.0 (mL/vial) = 2 vials

6.2.2 Study Drug Administration

Each treatment cycle will span 28 days, with durvalumab administered on Day 1 and AZD6738 administered on Days 15 to 28 inclusive.

Administration of AZD6738

When AZD6738 is administered, patients must fast (water to drink only) for at least 2 hours prior to taking a dose, to at least 1 hour post-dose for all doses.

AZD6738 will be administered orally 240 mg twice daily, approximately 12 hours apart, starting on Day 15 until Day 28 of each durvalumab treatment cycle, starting with Cycle 1.

Patients must receive AZD6738 for 14 days within a 28-day durvalumab cycle. A durvalumab cycle must not be < 28 days. Once started, AZD6738 must not be given on any other days of the cycle, and dosing days must stay relative to the durvalumab administration on Day 1 of each cycle. AZD6738 can be given without durvalumab in each cycle **only** if durvalumab has been permanently discontinued, in which case dosing days for AZD6738 remain Day 15 to Day 28 of each 4-week cycle. In case of AZD6738 interruption within the planned Day 15 to 28 dosing window (for any reason), resumption of treatment can only take place within the planned dosing window and not beyond, even if this means the subject receives less than the specified 14 days AZD6738 dosing in the particular cycle. In case remaining toxicity would prohibit the onset of AZD6738, a maximum delay of 28 days is allowed.

Patients are allowed to take the scheduled dose up to 2 hours after the scheduled dose time. If greater than 2 hours, the missed dose should not be taken and patient should continue with next dose at allotted time. If patient wishes to bring forward the time of their scheduled dose, the dose can be taken up to a maximum of 2 hours prior to the scheduled time, ie, ± 2-hour window.

Administration of durvalumab

Following preparation of durvalumab (see Section 6.2.1), the entire contents of the IV bag should be administered as an IV infusion over approximately 60 minutes (± 15 minutes).

Patients should continue to receive study treatment (ie, durvalumab in combination with AZD6738) until objective radiological disease progression as per Response Evaluation Criteria in Solid Tumours (RECIST 1.1), as long as, in the Investigator's opinion, they are benefiting from treatment and they do not meet any other discontinuation criteria. Disease progression should be confirmed by a subsequent scan (no earlier than 4 weeks later) in the absence of clinically significant deterioration as assessed by the Investigator. All patients who have objective progression of disease will enter follow-up.

6.2.3 Storage

All study drugs should be kept in a secure place under appropriate storage conditions.

The AZD6738 product label on the bottle specifies the appropriate storage.

Durvalumab is to be stored at the study centre in a secured facility with limited access and controlled temperature (2ºC to 8ºC). The study drug storage temperature should be monitored on a daily basis and documented in the temperature monitoring log according to the study drug handling instructions.

The study drug must be kept in the original outer container and under conditions specified on the labels.

In the following cases, the centre staff should not use affected study drug and should immediately contact AstraZeneca representative for further guidance:

- Temperature excursion upon receipt or during storage at the study
- Damaged kit upon receipt
- Damaged vial/bottle

Damaged study drug should be documented according to the instructions provided by AstraZeneca representative. Storage conditions stated in the IB, or the study drug Handling Instructions document, may be superseded by the label storage.

6.2.4 Accountability

The study drugs provided for this study should only be used as directed in the study protocol.

The study site staff will account for all study drugs received at the centre, for unused study drugs, and for appropriate destruction (according to local procedures). Certificates of delivery, destruction, and/or return should be signed.

The administration of all medications (including study drug) and details of treatment with study drug should be recorded in the appropriate sections of the electronic Case Report Form (eCRF).

6.3 Measures to Minimise Bias: Randomisation and Blinding

This is an open-label study.

Recruitment into the biomarker non-matched arms will be conducted in a sequential manner.

If a patient withdraws from participation in the study, then his/her enrolment code cannot be reused. Withdrawn patients will not be replaced.

6.4 Treatment Compliance

The administration of all study drugs should be recorded in the appropriate sections of the eCRF. Durvalumab will be administered on site. Treatment compliance will be assured by reconciliation of site drug accountability logs. Patients will record their oral AZD6738 dosing on a diary which should be returned to the site at the next available visit. Sites should additionally record AZD6738 doses taken at site visits.

Patients will self-administer AZD6738. Patients should be given clear instructions on how and when to take their study treatment. Study site staff will make tablet counts at regular intervals during treatment, when the bottles are returned per cycle. Compliance will be assessed by the tablet count and the information will be recorded in the appropriate section of the eCRF. After

the tablet count has been performed, the remaining tablets will not be returned to the patient but will be retained by the investigative site until reconciliation is completed by the study monitor. All patients must return their bottle(s) of AZD6738 at the appropriate study visit. Patients will be instructed to notify study site personnel of missed doses. Dates of missed or held doses will be recorded by the patient on their patient diary and by the site staff on the eCRF.

Patients must return all containers and any remaining tablets at their next scheduled treatment cycle and at the end of the study.

Any change from the dosing schedule, dose interruptions, dose reductions, dose discontinuations should be recorded in the eCRF. Note: Dose reductions are not allowed for durvalumab (see Section 6.6).

The Study Drug Storage Manager is responsible for managing the study drug from receipt by the study site until the destruction or return of all unused study drug. The Investigator(s) is/are responsible for ensuring that the patient has returned all unused study drug.

Use of study treatment in doses in excess of that specified in the protocol is considered to be an overdose. Refer to Section 8.4.3 of the core protocol for procedures in case of overdose.

6.5 Concomitant Therapy

Any medication or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the patient is receiving at the time of enrolment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Prohibited concomitant medications are described in Table 3. Please refer to Section 8.4.5 for guidance on management of study drug-related toxicities.

The use of concomitant medications must be recorded in the eCRF.

Table 3 Prohibited Medications

Prohibited Medication/Class of Drug:	
Unless stated otherwise, these medications are prohibited from the time that patients enter the main screening period until the last dose of study treatment. The pre-screen may be done whilst on prior therapy.	
Any investigational anticancer therapy other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment

Table 3 Prohibited Medications

Prohibited Medication/Class of Drug:	Module 9 (HUDSON)
Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment. (Note: concurrent use of hormones for non-cancer-related conditions [eg, insulin for diabetes and hormone replacement therapy] is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable [eg, by local surgery or radiotherapy]). Patients may receive treatment with bisphosphonates or RANKL inhibitors for the treatment of bone metastases
Immunosuppressive medications, including, but not limited to: systemic corticosteroids at doses exceeding 10 mg/day of prednisone or its equivalent, methotrexate, azathioprine, and tumour necrosis factor-α blockers	Should not be given concomitantly, or used for premedication prior to the infusions. The following are allowed exceptions: • Use of immunosuppressive medications for the management of study drug-related AEs • Short-term premedication for patients receiving combinations where the prescribing information for the agent requires the use of steroids for documented hypersensitivity reactions • Use in patients with contrast allergies • In addition, use of inhaled, topical, and intranasal corticosteroids is permitted. A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of non-immunotherapy related events experienced by the patient (eg, chronic obstructive pulmonary disease, radiation, nausea, etc).
Live attenuated vaccines	Prohibited from the time that patients enter the main screening period until 180 days after the last dose of study treatment.
Epidermal growth factor receptor (EGFR) Tyrosine kinase inhibitors (TKIs)	Should not be given concomitantly. Should be used with caution in the 90 days post last dose of durvalumab. Increased incidences of pneumonitis (with third generation EGFR TKIs) and increased incidence of transaminase increases (with 1st generation EGFR TKIs) have been reported when durvalumab has been given concomitantly.
Herbal and natural remedies which may have immune-modulating effects	Should not be given concomitantly unless agreed by the sponsor

AE, adverse event

The use of herbal preparations/medications should be discouraged throughout the study. These herbal medications include, but are not limited to: St. John's Wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone, yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 7 days prior to first dose of study drug (3 weeks for St. John's Wort). Use of these products, as well as use of all vitamins, nutritional supplements and all prescribed concomitant medications, must be recorded in the eCRF.

Other concomitant treatment

Medication other than that described above, which is considered necessary for the patient's safety and wellbeing, may be given at the discretion of the Investigator and recorded in the appropriate sections of the eCRF.

6.5.1 Rescue and Supportive Medication

The study site will supply rescue medication, and this will be procured locally. The sponsor will supply only if required by local regulations.

The use of rescue medications is allowable at any time during the study. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

Supportive medication, described in Table 4, may be given at the discretion of the Investigator and recorded in the appropriate sections of the eCRF.

Table 4 Supportive Medication

Supportive Medication/Class of Drug:	Usage:
Concomitant medications or treatments (eg, acetaminophen or diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care, except for those medications identified as "prohibited," as listed above	To be administered as prescribed by the Investigator
Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy to non-target lesions, etc])	Should be used, when necessary, for all patients AZD6738 treatment should be discontinued for a minimum of 3 days before a patient undergoes palliative radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.
Inactivated viruses, such as those in the influenza vaccine or authorised and approved COVID-19 vaccines.	Permitted. Administration of COVID-19 vaccines should be avoided for 72 hours prior to administration of the first dose of study treatment.

COVID-19 Coronavirus Disease 2019.

6.5.2 Effect of AZD6738 on Other Drugs

Avoid concomitant medications, herbal supplements and/or ingestion of foods that significantly modulate CYP[redacted] or [redacted] activity (see guidelines below). Note: These include common azole antifungals, macrolide antibiotics, etc. In the absence of discontinuation criteria, if the Investigator feels that concomitant administration of medications, herbal supplements or foods that significantly modulate CYP[redacted] activity is necessary based upon medical judgement, such products may be administered with caution following discussion between the Investigator and the study physician.

Concomitant medication may be given as medically indicated with the following exceptions:

- The principal enzyme for metabolising AZD6738 is CYP[CCI]. Patients should avoid concomitant drugs, herbal supplements, and/or ingestion of foods known to modulate CYP3A4 activity from the time they enter the screening period until 28 days after the last dose of study medication.
- AZD6738 is an inducer of CYP[CCI], CYP[CCI] and CYP[CCI] and showed weak inhibition of CYP[CCI] CYP[CCI] and CYP[CCI] Caution should be applied with co-administration of drugs that are either completely metabolised by CYP3A4 and/or CYP1A2, CYP2C8 or CYP[CCI] or that are substrates of CYP[CCI] and/or CYP[CCI] CYP[CCI] and CYP[CCI] and also have a narrow therapeutic index. Investigators should be aware that the exposure of other drugs metabolised by CYP[CCI] CYP[CCI] and/or CYP[CCI] may be increased and exposure of other drugs metabolised by CYP[CCI] and/or CYP[CCI] may be reduced.
- Strong CYP[CCI] inducers. For patients taking any of these drugs the required washout periods prior to starting AZD6738 is 2 weeks, except for St. John's Wort, which is 3 weeks.
- Prior to study medication, use of potent inducers or inhibitors of CY[CCI] are not permitted. For subjects taking any of these drugs, the required wash-out periods before starting AZD6738 is 5 half-lives; except for St. John's Wort, which is 3 weeks.
- On study medication, if there is no suitable alternative concomitant medication other than a potent inhibitor of CYP[CC], the Investigator must interrupt AZD6738 for the duration of the potent CYP[CC] inhibitor and wait for the required wash-out period (5 half-lives) before dosing AZD6738 again. If potent CYP[CC] inducers are considered necessary for the patient's safety and welfare, this may diminish the clinical efficacy of AZD6738 and the patient should be monitored carefully for any change in the efficacy of study treatment.
- AZD6738 is also a [CCI] substrate. Co-administration of [CCI] inhibitors or inducers may affect exposure to AZD6738 and therefore should not be co-administered with AZD6738. If the use of any inhibitors or inducers of [CCI] are considered necessary for the patient's safety and welfare, the Investigator must interrupt AZD6738 for the duration of the [CCI] inhibitor or inducer and wait for the required wash-out period of the P-gp modulator (five half-lives) before dosing with AZD6738.
- AZD6738 is a substrate of [CCI] Co-administration of [CCI] inhibitors or inducers may affect exposure to AZD6738; therefore, it is recommended that the Investigators must interrupt AZD6738 for the duration of the BCRP inhibitor or inducer and wait for the required wash-out period of the [CCI] modulator (5 half-lives) before dosing AZD6738 again.
- AZD6738 is an inhibitor of [CCI]. Co-administration of substrates of [CCI] may affect exposure to AZD6738; therefore, it is recommended that caution should be applied when such drugs are to be administered with AZD6738.
- The use of any herbal supplements or other 'folk remedies' (and medications and foods that significantly modulate CYP[CC]) should be discouraged. If deemed necessary, such products may be administered with caution and the reason for use documented in the eCRF.
- Anticoagulation therapy: patients on warfarin may participate in this study but it is recommended that their INR is monitored more frequently.

6.6 Dose Modification and Discontinuation

For patients who weigh ≥ 30 kg, the dose of durvalumab cannot be modified. If a patient's body weight falls below 30 kg during the study, (s)he will be withdrawn from the study treatment unless (s)he derives some clinical benefit according to the treating physician. In this case, and following agreement between the treating physician and the Sponsor, the patient may continue treatment at a body-weight adapted dose of 20 mg/kg actual body weight.

Durvalumab dosing can be interrupted in the event of treatment-related toxicity. All toxicities will be graded according to CTCAE version 4.03. Dose reductions are not permitted. In case of doubt, the Investigator should consult with the study physician. Please refer to the toxicity management guidelines for durvalumab.

Dose adjustments for AZD6738 (Table 5) will be based on the organ system exhibiting the greatest degree of toxicity. Dose reductions or interruptions, and initiation of supportive care, are allowed as deemed appropriate by the treating physician. If Day 1 treatment with durvalumab is delayed, then AZD6738 will not resume until 14 days after the next durvalumab dose (see Section 6.2.2).

The maximum interruption or cycle delay for starting AZD6738 that is permitted is 42 days and the onset of the subsequent durvalumab administration will need to be delayed accordingly. Any patient requiring a toxicity related dose delay of more than 42 days from the last day of dosing must be discontinued from the study unless there is approval from the study physician for the patient to continue. A patient may continue on monotherapy if the other treatment is permanently stopped (core protocol Section 7.1.1).

Study treatment should be stopped at least 3 days prior to planned surgery. After surgery study treatment can be restarted when the wound has healed. No stoppage of study treatment is required for any biopsy procedure.

Table 5 AZD6738 Dose Modifications for Toxicity Management

Dose level	AZD6738
Initial dose	240 mg twice daily Days 15-28
Level 1 dose reduction	160 mg twice daily Days 15-28
Level 2 dose reduction	120 mg twice daily Days 15-28
Level 3 dose reduction	80 mg twice daily Days 15-28
Level 4 dose reduction	Stop treatment

Management of study drug-related toxicities is described in detail in Section 8.4.5.

Patients who develop an event of ≥ Grade 3 of thrombocytopenia, anaemia, and/or neutropenia later than Cycle 2 in their treatment will need to have additional assessment on Day 22 (± 1 day window) until there is no evidence of ≥ Grade 3 thrombocytopenia, anaemia, and/or neutropenia for at least 2 cycles.

6.7 Treatment After the End of the Study

Patients are permitted to either receive standard of care therapy, or to continue to receive study treatment following the end of the study if, in the opinion of the Investigator, they are continuing to receive benefit from treatment. After discontinuation of study treatment, the Investigator will be at liberty to define further most appropriate anti-cancer treatment. Subsequent anti-cancer treatment is expected to be initiated following the cancer recurrence or development of a new cancer. Information on subsequent anti-cancer therapies should be recorded on the clinical database.

7. DISCONTINUATION OF TREATMENT AND PATIENT WITHDRAWAL

Please refer to Section 7 in the core protocol.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in the SoA (Table 1).

8.1 Efficacy Assessments

Please refer to the core protocol.

8.2 Safety Assessments

8.2.1 Clinical Safety Laboratory Assessments

Please refer to core protocol.

8.2.1.1 Coagulation

Please refer to core protocol.

8.2.1.2 Other Safety Assessments

Please refer to core protocol.

8.2.1.3 Pneumonitis (Interstitial Lung Disease) Investigation

The following assessments, and additional assessments if required, will be performed to enhance the investigation and diagnosis of potential cases of pneumonitis. The results of the assessment will be collected.

- Physical examination; Signs and symptoms (cough, shortness of breath and pyrexia, etc) including auscultation for lung field will be assessed.
- SpO_2; Saturation of peripheral oxygen (SpO_2)
- Other items; When pneumonitis (interstitial lung disease [ILD]) is suspected during study treatment, the following markers should be measured where possible:
  - ILD markers (KL-6, SP-D) and β-D-glucan
  - Tumour markers: Particular tumour markers which are related to disease progression.

8.2.2 Physical Examinations

Please refer to core protocol.

8.2.3 Vital Signs

Please refer to section 8.2.3 in the core protocol. However, if clinically indicated, eg, in the event of clinically relevant symptoms such as pre-syncope or dizziness, blood pressure will be measured in the supine and standing positions after at least 10 minutes' rest. Assessments will be performed at the visits as shown in the SoA (Table 1).

8.2.4 Electrocardiograms

Please refer to core protocol.

8.2.5 Performance Status

Please refer to core protocol.

8.3 Collection of Adverse Events

Please refer to the core protocol.

8.4 Safety Reporting and Medical Management

8.4.1 Reporting of Serious Adverse Events

Please refer to the core protocol.

Any myeloid malignancies (ie., MDS and/or AML) should be reported whenever this has been observed in the follow-up of the patients.

8.4.2 Pregnancy

Please refer to the core protocol.

8.4.3 Overdose

Please refer to the core protocol.

8.4.4 Medication Error

Please refer to the core protocol.

8.4.5 Management of Study Drug-related Toxicities

8.4.5.1 Management of Durvalumab-related Toxicities

Please refer to the toxicity management guidelines for durvalumab.

8.4.5.2 Management of AZD6738-related Toxicities

If a patient experiences a clinically significant and/or unacceptable toxicity dosing will be interrupted and supportive therapy administered as required.

If the toxicity resolves or reverts to CTCAE v4.03 Grade ≤ 1 or 2 (depending on the toxicity), treatment with AZD6738 may be restarted using the rules in Table 6 for dose modifications. Patients who are at the lowest possible dose, or who had their dose previously reduced to the lowest possible dose and who have demonstrated an acceptable response to the dose interruption may be permitted to restart at the lowest dose level at the discretion of the Investigator.

If the toxicity does not resolve to CTCAE Grade ≤ 1 or 2 or the patient is not showing clinical benefit, then the patient should be discontinued from treatment and observed until resolution of the toxicity.

Any patient requiring a toxicity related dose delay of more than 42 days from the last day of dosing must be discontinued from the study unless there is approval from the study physician for the patient to continue.

If a patient develops severe haematologic toxicity or blood transfusion dependence, treatment with AZD6738 should be interrupted and appropriate haematologic testing should be initiated. If the blood parameters remain clinically abnormal after 4 weeks of AZD6738 dose interruption, bone marrow analysis and/or blood cytogenetic analysis are recommended. If myeloid malignancies are confirmed whilst on treatment with AZD6738, it is recommended that AZD6738 should be discontinued and the patient be treated appropriately. AEs of myeloid malignancies should be monitored by conventional AE collection and reporting, additionally any cases should be reported after the 30-day follow-up period irrespective of Investigator causality.

The dose of AZD6738 must not be adjusted under any other circumstances than those described in this section unless prior agreement is given by the Sponsor.

All dose modifications and interruptions (including any missed doses) and the reasons for the modifications/interruptions are to be recorded in the eCRF.

Table 6 Dose Interruption and Stopping Criteria (14-day schedule)

Event	Action
Grade 1 neutropenia and/or thrombocytopenia	AZD6738 dosing may continue if neutrophil count is ≥ 1500/mm^3 and/or platelet count is ≥ 75000/mm^3.
Grade 1-2 toxicities (except neutropenia and thrombocytopenia)	Investigator decision whether to interrupt AZD6738 (max 28 days) or continue treatment. Treatment may be resumed at the same dose level or with a dose reduction by 1 level.
Grade 2 neutropenia or Grade 3 anaemia	Interrupt AZD6738 (max 28 days) and give appropriate supportive treatment eg, transfusion, until AE improves to at least neutrophil count ≥ 1500/mm^3 and haemoglobin ≥ 8.0 g/dL, then restart reducing the dose of AZD6738 by 1 level[a]. If a further dose reduction is required after the level 3 dose reduction, the patient must stop treatment.
Grade 2-3 thrombocytopenia	**First occurrence** Interrupt AZD6738 only (max 28 days) and give appropriate supportive treatment until platelets improve to at least ≥ 100000/mm^3. At resolution, it is not mandatory to lower the dose as blood counts may recover during the "off period" on the intermittent schedule. If blood counts do not recover by the start of the next dosing period, AZD6738 should be restarted with a dose reduction by 1 level[a] for AZD6738. **Subsequent occurrences** Interrupt AZD6738 only (max 28 days) and give appropriate supportive treatment. Treatment may be restarted with a reduced dose of AZD6738 when the toxicity is resolved, or treatment may be stopped at the Investigator's discretion.
Grade 4 thrombocytopenia	Interrupt AZD6738 (max 28 days) and give appropriate supportive treatment; Investigator discretion on whether to restart treatment with a dose reduction by 1 dose level[a] for AZD6738 when the platelet count has recovered to ≥ 100000/mm^3 or stop treatment.
Grade 3-4 toxicity (including Grade 3-4 neutropenia or Grade 4 anaemia) *Excludes* Grade 3 anaemia or Grade 3-4 thrombocytopenia (see above)	**First occurrence** Interrupt AZD6738 (max 28 days) and give appropriate supportive treatment; restart treatment with a dose reduction by 1 level[a] for AZD6738 when the toxicity is resolved (Grade 1 or 2 depending on the toxicity or returns to baseline). **Subsequent occurrences** Investigator discretion on whether to interrupt AZD6738 (max 28 days) or to stop treatment. Restart treatment with an AZD6738 dose reduction of 1 or 2 levels. If a further dose reduction is required after the level 3 dose reduction, the patient must stop treatment.
Vomiting	If vomiting occurs shortly after AZD6738 is swallowed, the dose should only be replaced if all of the intact tablets can be counted. Resume with the following scheduled dose.

Table 6 Dose Interruption and Stopping Criteria (14-day schedule)

Event	Action
Missed dose	Allowed to take the scheduled dose up to 2 hours after the scheduled dose time. If greater than 2 hours, the missed dose should not be taken and the patient should continue with next dose at the allotted time.

[a] This table is for guidance. Therefore, for example, it may be deemed appropriate by the Investigator to reduce the dose by more than 1 dose level depending on the individual patient circumstances.

Individual stopping criteria:

Hepatic

- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) or ALP* > 5 × ULN
- ALT or AST or ALP* > 3 × ULN with the appearance of symptoms associated with a clinical diagnosis of hepatitis including right upper quadrant pain or tenderness, fever, rash or eosinophilia (> 5%)
- [ALT or AST > 3 × ULN] and [total bilirubin > 2 × ULN or INR+ > 1.5 or other evidence of impairment to the synthesis function of the liver]

* In the presence of bone metastasis, assess bone specific isoform of raised ALP in the presence of a raised gamma-GT (to ensure the ALP change is specific to the liver).
\+ Unless patient is receiving warfarin.

Please refer to Appendix E "Actions required in increases in liver biochemistry and evaluation of Hy's Law".

Cardiovascular

Clinically significant hypotension defined as an asymptomatic decrease of more than 20 mmHg in systolic blood pressure to below 70 mmHg persisting for at least 10 minutes.

Symptomatic orthostatic fall in systolic blood pressure of more than 20 mmHg compared to resting supine systolic blood pressure.

Haematologic

Patients with suspected or with indications of MDS and/or AML must have the dose of AZD6738 stopped under all circumstances, and evidence of AML/MDS should be ruled out. Further treatment can only be accepted after discussion and agreement with the sponsor.

8.5 Pharmacokinetics

Refer to the core protocol.

8.6 Pharmacodynamics

Pharmacodynamic parameters will be evaluated in this study (see Section 8.6 of the core protocol).

8.7 Genetics

Refer to the core protocol.

8.8 Biomarkers

Refer to the core protocol.

8.9 Medical Resource Utilisation and Health Economics

Medical Resource Utilisation and Health Economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

Refer to the core protocol.

10. REFERENCES

Cimprich and Cortez 2008
Cimprich KA, Cortez D. ATR: an essential regulator of genome integrity. Nat Rev Mol Cell Biol. 2008;9:616-27.

Galluzzi et al 2012
Galluzzi L, Senovilla L, Zitvogel L, Kroemer G. The secret ally: immunostimulation by anticancer drugs. Nat Rev Drug Discov. 2012;11(3):215-33

Garassino et al 2017
Garassino M, Vansteenkiste J, Joo-Hang K, Hervé L, Mazières J, Powderly J et al. PL04a.03: Durvalumab in ≥3rd-Line Locally Advanced or Metastatic, EGFR/ALK Wild-Type NSCLC: Results from the Phase 2 ATLANTIC Study. J Thor Onc. 2017;12:S10-S11.

Mellman et al 2011
Mellman I, Coukos G, Dranoff G. Cancer immunotherapy comes of age. Nature. 2011;480:480-9.

Narwal et al 2013
Narwal R, Roskos LK, Robbie GJ. Population pharmacokinetics of sifalimumab, an investigational anti-interferon alpha monoclonal antibody, in systemic lupus erythematosus. Clin Pharmacokinet. 2013;52:1017–27.

Ng et al 2006
Ng CM, Lum BL, Gimenez V, Kelsey S, Allison D. Rationale for fixed dosing of pertuzumab in cancer patients based on population pharmacokinetic analysis. Pharm Res. 2006;23(6):1275–84.

O'Connor 2015
O'Connor MJ. Targeting the DNA Damage Response in Cancer. Mol Cell. 2015;60:547-60.

Parkes et al 2017
Parkes EE, Walker SM, Taggart LE, McCabe N, Knight LA, Wilkinson R et al. Activation of STING-dependent innate immune signaling by S-Phase-specific DNA damage in breast cancer. J Natl Cancer Inst. 2017;109(1).

Stewart et al 2015
Stewart R, Morrow M, Hammond SA, Mulgrew K, Marcus D, Poon E et al. Identification and characterization of MEDI4736, an antagonistic anti-PD-L1 monoclonal antibody. Cancer Immunol Res. 2015;3(9):1052-62.

Toledo et al 2011
Toledo LI, Murga M, Zur R, Soria R, Rodriguez A, Martinez S et al. A cell-based screen identifies ATR inhibitors with synthetic lethal properties for cancer-associated mutations. Nat Struct Mol Biol. 2011;18:721-7.

Villaruz et al 2016
Villaruz LC, Jones H, Dacic S et al. ATM protein is deficient in over 40% of lung adenocarcinomas. Oncotarget 2016;7(36):57714-57725.

Wang et al 2009
Wang DD, Zhang S, Zhao H, Men AY, Parivar K. Fixed dosing versus body size based dosing of monoclonal antibodies in adult clinical trials. J Clin Pharmacol 2009;49(9):1012–24.

Weber and Ryan 2015
Weber AM, Ryan AJ. ATM and ATR as therapeutic targets in cancer. Pharmacol Ther 2015;149:124-38.

Zhang et al 2012
Zhang S, Shi R, Li C, Parivar K, Wang DD. Fixed dosing versus body size-based dosing of therapeutic peptides and proteins in adults. J Clin Pharmacol 2012;52(1):18–28.

11. AZD6738 DRUG-DRUG INTERACTIONS

Restrictions regarding drugs affecting CYP[redacted] metabolism

There are currently no data confirming that there is a PK interaction between drugs that affect CYP[redacted] metabolism and AZD6738; a potential interaction is considered on the basis of preclinical and in vitro data only. AZD6738 is predominantly eliminated via CYP[redacted] metabolism, therefore CYP[redacted] inhibitors or inducers may increase or decrease exposure to AZD6738, respectively. Potent inhibitors or inducers of CYP[redacted] should not be combined with AZD6738. In vitro data also suggest that AZD6738 may be metabolised by CYP[redacted] to a lesser extent, therefore caution should be applied with co-administration of potent inhibitors or inducers of CYP[redacted]

Drugs known to be inhibitors and inducers of CYP[redacted] or CYP[redacted] are listed in Table 7 and Table 8, respectively. These lists are not intended to be exhaustive, and similar restrictions will apply to other agents that are known to modulate CYP[redacted] or CYP[redacted] activity. Please contact AstraZeneca with any queries on this issue. Please refer to full prescribing information for all drugs prior to co-administration with AZD6738.

Table 7 Drugs Known to be Inhibitors and Inducers of CYP[redacted]

Potent CYP[redacted] inhibitors	Potent CYP[redacted] inducers
boceprevir	apalutamide
ceritinib	avasimibe
clarithromycin	carbamazepine
cobicistat (GS-9350)	ceralasertib
conivaptan	enzalutamide
danoprevir / RIT	ivosidenib
elvitegravir / RIT	lumacaftor
grapefruit juice[a]	mitotane
idelalisib	phenobarbital
indinavir	phenytoin
indinavir /RIT	rifampin
itraconazole	rifapentine
ketoconazole	St John's Wort extract
LCL161	
lopinavir / RIT	
mibefradil	
mifepristone	
nefazodone	
nelfinavir	
posaconazole	
ribociclib	
ritonavir	
saquinavir	
saquinavir / RIT	
telaprevir	
telithromycin	
tipranavir/RIT	
troleandomycin	
VIEKIRA PAK2[b]	
voriconazole	

[a] Double-strength grapefruit juice. Patients should abstain from eating large amounts of grapefruit and Seville oranges (and other products containing these fruits eg, grapefruit juice or marmalade) during the study (eg, no more than a small glass of grapefruit juice (120 mL) or half a grapefruit or 1 to 2 teaspoons (15 g) of Seville orange marmalade daily

[b] VIEKIRA PAK = 150/100 mg paritaprevir/ritonavir + 25 mg ombitasvir + 800 mg dasabuvir for 28 days.

List created using the University of Washington Drug-Drug Interaction Database July 2019.

RIT Ritonivir. Ritonavir has dual effects of simultaneous CYP[redacted] inhibition and induction, and the net pharmacokinetic outcome during chronic ritonavir therapy is inhibition of CYP[redacted] activity

Table 8 Drugs Known to be Inhibitors and Inducers of CYP[redacted]

Potent CYP2C8 inhibitors	Potent CYP[redacted] inducers
gemfibrozil clopidogrel	None identified

List created using the University of Washington Drug-Drug Interaction Database Jan 2020.

Drugs known to be inhibitors or inducers of [redacted] undertake appropriate monitoring if co-administration is necessary

AZD6738 is a substrate of [redacted]. Co-administration of [redacted] inhibitors/inducers or [redacted] inhibitors/inducers may affect exposure to AZD6738, therefore it is recommended that these are not co-administered with AZD6738.

Drugs known to be inhibitors or inducers of [redacted] are listed in Table 9 and Table 10, respectively. These lists are not intended to be exhaustive, and similar restrictions will apply to other agents that are known to modulate [redacted]. Please contact AstraZeneca with any queries on this issue. Please refer to full prescribing information for all drugs prior to co-administration with AZD6738.

Table 9 Drugs Known to be Inhibitors or Inducers of CCI

Drugs Known to be Inhibitors of CCI	Drugs Known to be Inducers of CCI
alogliptin	apalutamide
amiodarone	avasimibe
asian ginseng (Panax ginseng)	carbamazepine
asunaprevir	danshen (Salvia miltiorrhiza)
AZD5672	efavirenz
azithromycin	genistein
canagliflozin	green tea
captopril	phenytoin
carvedilol	quercetin
clarithromycin	rifabutin
clopidogrel	rifampin
cobicstat	ritonavir
conivaptan	St. John's wort extract
cremophor EL	tivantinib
cremophor RH	
curcumin	
daclatasvir	
daclatasvir/asunaprevir/beclabuvir	
diltiazem	
diosmin	
dronedarone	
elagolix	
eliglustat	
erythromycin	
felodipine	
five-flavor berry (schisandra chinensis)	
flibanserin	
fluvoxamine	
fostamatinib	
ginkgo	
glecaprevir/pibrentasvir	
indinavir	
indinavir/ritonavir	
isavuconazole	
itraconazole	
ivacaftor	
ketoconazole	
lapatinib	
lopinavir/ritonavir	
mibefradil	

mifepristone	
milk thistle	
mirabegron	
nelfinavir	
neratinib	
nifedipine	
nitrendipine	
osimertinib	
paritaprevir/ritonavir/ombitasvir	
paroxetine	
piperine	
propafenone	
quercetin	
quinidine	
quinine	
ranolazine	
rifampin	
ritonavir	
rolapitant	
rucaparib	
saquinavir/ritonavir	
sarecycline	
simeprevir	
sofosbuvir/velpatasvir/voxilaprevir	
St. John's wort extract	
surfactant TPGS	
suvorexant	
talinolol	
telithromycin	
telaprevir	
telmisartan	
tezacaftor/ivacaftor	
ticagrelor	
tipranavir/ritonavir	
tolvaptan	
valbenazine	
valspodar (PSC 833)	
vandetanib	
velpatasvir	
vemurafenib	
verapamil	
voclosporin	

vorapaxar	

List created using the University of Washington Drug-Drug Interaction Database October 2019.

Table 10 Drugs Known to be Inhibitors or Inducers of [redacted]

Drugs Known to be Inhibitors of [redacted]	Drugs Known to be inducers of [redacted]
afatinib	Please check individual drugs on a case by case basis
aripiprazole	
curcumin	
cyclosporine	
elacridar	
erlotinib	
fluvastatin	
fumitremorgin	
gefitinib	
ivermectin	
lapatinib	
nilotinib	
novobiocin	
pantoprazole	
pitavastatin	
ponatinib	
quercetin	
quizartinib	
rabeprazole	
regorafenib	
rilpivirine	
sulfasalazine	
sunitinib	
tacrolimus	
teriflunomide	
trametinib	
trifluoperazine	
vismodegib	
eltrombopag	
atazanavir	
lopinavir	
ritonavir	
tipranavir	
omeprazole	
estrone	
17b-estradiol	
imatinib mesylate	

List created using http://dmd.aspetjournals.org/content/dmd/43/4/490.full.pdf
Note: Although CCI is involved in a number of clinically relevant DDIs, none of the listed inhibitors above is truly specific for this transporter

Drugs known to be substrates of CYPCCI and/or CYPCCI or CYPCCI or CYPCCI undertake appropriate monitoring if co-administration is necessary

AZD6738 is an inducer of CYPCCI CYPCCI and CYPCCI and showed weak inhibition of CYPCCI CYPCCI and CYPCCI Therefore, caution should be applied with co-administration of drugs that are either completely metabolised by CYPCCI and/or CYPCCI CYPCCI or CYPCCI or that are substrates of CYPCCI and/or CYPCCI CYPCCI and CYPCCI and also have a narrow therapeutic index (Table 11). Investigators should be aware that the exposure of other drugs metabolised by CYPCCI CYPCCI and/or CYPCCI may be increased and exposure of other drugs metabolised by CYPCCI and/or CYPCCI may be reduced.

Table 11 Drugs Known to be Metabolised by CYPCCI and/or CYPCCI CYPCCI and CYPCCI

Metabolised by CYPCCI	Metabolised by CYPCCI	Metabolised by CYPCCI	Metabolised by CYPCCI
Abemaciclib (NTR)		daprodustat	benzbromarone
ABT-384	agomelatine	dasabuvir	celecoxib
Acalabrutinib (NTR)	alosetron[a]	repaglinide[b]	ibuprofen
alfentanil	caffeine		(R)-ibuprofen
alisporivir	duloxetine		(S)-ibuprofen
almorexant	melatonin		glimepiride
alpha-dihydroergocryptine	pirfenidone		glipizide
aplaviroc	ramelteon[a]		lornoxicam
aprepitant	selegiline[a]		meloxicam
asunaprevir	tacrine		piroxicam
atazanavir	tasimelteon[a]		(S)-warfarin
atorvastatin	tizanidine (NTR)		(NTR)
avanafil			tolbutamide
avapritinib			
AZD1305			
BIRL 355			
blonanserin			
bosutinib (NTR)			
brecanavir			
brotizolam			
budesonide			
buspirone			
BZF961			
capravirine			

casopitant cobimetinib (NTR) conivaptan (NTR) danoprevir darifenacin darunavir dasatinib (NTR) dronedarone ebastine eletriptan eliglustat (in subjects CYP[redacted] PMs) elvitegravir entrectinib (NTR) eplerenone everolimus felodipine ibrutinib indinavir isavuconazole itacitinib ivabradine ivacaftor L-771,688 Levomethadyl/Levacetymethadol (LAAM) (NTR) Lomitapide (NTR) lonafarnib lopinavir lovastatin lumefantrine lurasidone maraviroc midazolam midostaurin (NTR) morphothiadin naloxegol neratinib (NTR) nisoldipine paritaprevir4 perospirone pyrotinib quetiapine			

ridaforolimus			
saquinavir			
sildenafil			
simeprevir			
simvastatin			
sirolimus			
tacrolimus			
terfenadine			
ticagrelor			
tilidine3			
tipranavir			
tolvaptan (NTR)			
triazolam			
ubrogepant			
ulipristal			
vardenafil			
venetoclax (NTR)			
vicriviroc			
vilaprisan			
voclosporin			
zanubrutinib (NTR)			

[a] Complex Interaction -Substrates metabolized by multiple enzymes, including CYP CCI

[b] Repaglinide is also a substrate of CCI which might also be inhibited by gemfibrozil or its glucuronide.

List created using the University of Washington Drug-Drug Interaction Database October 2019. Note: This is not an exhaustive list.
(NTR) drug listed in the Narrow Therapeutic Index list by CYP isoform in DrugBank.

Drugs known to be substrates of CCI undertake appropriate monitoring if co-administration is necessary

AZD6738 is also an inhibitor of CCI Caution should be applied with co-administration of substrates of CCI as AZD6738 may increase their exposure.

Drugs known to be substrates of CCI are listed in Table 12 and Table 13, respectively. These lists are not intended to be exhaustive and appropriate medical judgment is required. Please contact AstraZeneca with any queries on this issue. Please refer to full prescribing information for all drugs prior to co-administration with AZD6738.

Table 12 Drugs Known to be Substrates of CCI

docetaxel
enalapril
olmesartan
phalloidin
repaglinide
statins[a]
temocaprilat
valsartan

[a] All statins.

List created using https://www.solvobiotech.com/transporters/CCI latest access Nov 2019.

Table 13 Drugs Known to be Substrates of CCI

anthracyclines
chlorothiazide
daunorubicin
doxorubicin
imatinib
irinotecan
methotrexate
mitoxantrone
nucleoside analogs
pantoprazole
prazosin
SN-38
topotecan
teriflunomide
rosuvastatin

List created using https://www.solvobiotech.com/transporters/bcrp, latest access Nov 2019.

Clinical Study Protocol

Drug Substance	Umbrella study
Study Code	D6185C00001 (HUDSON)
Version	14.0
Date	09 October 2024

Appendix R

Module 10: Durvalumab plus AZD6738

An Open-Label, Multi-Drug, Biomarker-Directed, Multi-Centre Phase II Umbrella Study in Patients with Non-Small Cell Lung Cancer, who Progressed on an Anti-PD-1/PD-L1 Containing Therapy (HUDSON**)**

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

Regulatory Agency Identification Numbers:

EudraCT number: 2017-002208-28

EU CT number: 2023-509004-15-00

IND number: 138050

VERSION HISTORY

Version 14.0, 09 October 2024
Key amendments and rationale for changes: **Section 2.2.2.2, AZD6738 data:** CCI [redacted] when AZD6738 is used as monotherapy and in combination with olaparib or durvalumab. **Table 2, study drug:** removed reference to Annex 13. **Section 6.5.2, effect of AZD6738 on other drugs; Section 11, AZD6738 drug-drug interactions:** Updated to describe AZD6738 as an inducer of CYPCCI CYPCCI and CYPCCI and a weak inhibitor of CYPCCI and CYPCCI **Section 8.4.1, reporting of serious adverse events:** addition of text relating to the reporting of MDS and/or AML during follow-up. **Section 8.4.5.2, management of AZD6738-related toxicities:** • Guidance was added for patients who experience suspected MDS/AML. • New sub-section was added to describe actions to be taken if a patient displays suspected indications of MDS and/or AML. **Table 8, drugs known to be inhibitors and inducers of CYPCC:** Ceralasertib was added as a potent CYPCC inducer. Minor text clarifications were also made.

Version 13.0, 14 December 2023
Key amendments and rationale for changes: **Front page:** EU CT number has been added in line with the core CSP. **Section 6.1.1, study drugs:** Text regarding 'Packaging and Labelling' updated to remove the information that labels will fulfil GMP Annex 13 requirements for labelling, as this Annex has been replaced.

Version 12.0, 01 March 2023

Key amendments and rationale for changes:

Table 1, schedule of activities:

- Updated to correct the matrix of the AZD6738 PK samples.
- Addition of a footnote to clarify the windows allowed for the administration of the study drugs.
- The window allowed to collect AZD6738 PK samples at Cycle 0 Day 7 and Day 28 was added to the applicable footnote.
- The time for collection of durvalumab PK samples was clarified.
- The footnote for the flow cytometry samples was changed to update the visit at which samples are to be collected and to clarify the number of patients to be sampled.

Section 2.2.1.2, durvalumab data: References for published studies were added.

Section 2.2.2.1, overview of AZD6738; Section 2.2.2.2 AZD6738 data: Updated in line with the AZD6738 IB Edition 11.

Section 4.3.1, justification for durvalumab dose: Added a cross-reference to the durvalumab IB for updates on data from ongoing studies.

Section 5.2, exclusion criteria (module 10-specific): Changed to align the exclusion criteria with the current AZD6738 project specific safety requirements (SSPR)

- Exclusion criterion R-4: Addition of text in bold:
  Inadequate bone marrow reserve or organ function as demonstrated by any of the following laboratory values: absolute neutrophil count <1.5 x 10^9/L; platelet count <100 x 10^9/L; haemoglobin <90 g/L, **with no blood transfusion (packed red blood cells) in the past 28 days.**
- Exclusion criterion R-6: Changed creatinine clearance from <45 mL/min to <40 mL/min

Table 2, study drugs; Section 6.2.1 durvalumab preparation and handling: The window for durvalumab infusion administration was clarified.

Section 6.2, preparation/handling/storage/accountability: Added a reference to the Pharmacy Manual.

Section 6.5.2, effect of AZD6738 on other drugs: Added cross-reference to Section 11 for details on AZD6738 drug-drug interactions.

Section 6.6, dose modification and discontinuation; 8.4.5.2 Management of AZD6738-related toxicities: Updated to clarify the procedures to follow after a study treatment dose delay.

Section 10, references: The list of references was updated in line with the citation in the text.

Section 11, AZD6738 drug-drug interactions: Section added, in line with Modules 8, 9, and 11.

In addition, minor typographical errors have been corrected throughout where applicable.

Version 11.0, 16 August 2022

Key amendments and rationale for changes:

Table 1, schedule of activities:

- Study week labelling clarified.
- Time window added to cycle days (where missing in error).
- AE/SAE monitoring and drug accountability rows corrected to include Days 7, 22 and 28 (where missing in error).
- Addition of lymphocyte and neutrophil counts to the haematology footnote to clarify these will be recorded as part of the routine white blood cell count for safety assessment.
- Footnote for additional assessments on Day 22 of Cycles 1 and 2 for detection of toxicity following the initial 7 days of AZD6738 dosing, updated to remove vital signs (not required).
- Footnote added to clarify that after Cycle 2, Day 22 and Day 28 site visits will be performed only for cycles where an AZD6738 PK sample is to be collected (Cycles 3, 4, 8 and 12), unless a patient has an event of thrombocytopenia, anaemia and/or neutropenia that is ≥ Grade 3 during the first 2 cycles, then only the Day 22 visit will be included for haematology and clinical chemistry assessments until there is no evidence of toxicity for at least 2 cycles.
- Removal of CCI sample collection on Day 22 (Cycles 1 and 2) and footnote added to clarify timing of sample collection. This change is made to align with other AstraZeneca projects.
- Footnote added for flow cytometry samples to clarify that if a sample is not collected at the screening (baseline) visit, there is no requirement to collect further samples for analysis at subsequent study visits as analysis requires a baseline result for comparison.

- Footnote added to clarify an on-treatment biopsy is not required if a fresh tumour sample is not collected at screening as analysis requires a baseline result for comparison (ie, from the pre-screening sample).

Figure 1, study design: Updated to remove survival follow-up of screen failures and associated footnote (collection of data is no longer required as of protocol amendment v10.0).

Section 5.2. exclusion criteria (Module 10-specific): Exclusion criterion 1 of the core protocol added as a new Module 10-specific exclusion criterion (R-1) to specify enrolled patients in Module 10 can proceed to main screening without waiting on central test results for pre-defined molecular aberrations. This addition is to allow patients in this module to start study treatment without waiting for central testing results when recruitment is only open to Group C modules.

Section 6.2.3, storage: Text is updated to clarify monitoring of temperature refers to study drug (durvalumab) storage.

In addition, minor typographical errors have been corrected and text clarifications not affecting interpretation have been made where applicable.

Version 10.0, 12 April 2022
Initial creation of Module 10. Version number 10.0 used for consistency with the rest of the protocol.

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

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1. PROTOCOL SUMMARY

1.1 Schedule of Activities (SoA)

The Schedule of Activities (SoA) for the lead-in and on-treatment period for Module 10 is shown in Table 1 below. For the SoA for the pre-screening and main screening visits, please refer to the core protocol.

Table 1 Schedule of Activities – Treatment intervention period (Module 10)

	Cycle 0 (7-day lead-in)		**C1** 28 days Weeks 1-4			**C2** 28 days Weeks 5-8			**C3 - etc** **All cycles 28 days**			**Study drug disc.** (28 days after study drug disc.)	**Safety follow-up** (90 days after study drug disc.)	**Survival follow-up**	**Notes**
Week	**1**		**1**	**4**		**5**	**8**		9, 13, 17 etc (Day 1 of each cycle)						
Day of cycle	**1**	**7**	**1**	**22**	**28**	**1**	**22**	**28**	**1**	**22[j]**	**28[j]**				
Window (days)	**0[a]**	**±2**	**±2**	**±2**	**-2**	**±2**	**±2**	**-2**	**±2**	**±2**	**-2**	**±7**	**±7**	**±7**	
Study procedures[c]															
Physical examination	X		X	X		X	X		X			X			Section 8.2.2 (core protocol)
Vital signs[b]	X		X	X[f]		X	X[f]		X			X			Section 8.2.3 (core protocol)
ECG	X		X			X			X						Section 8.2.4 (core protocol)
Concomitant medications	X		X	X		X	X		X			X			Section 6.5
Laboratory assessments[c]															
Clinical chemistry	X		X	X[f]		X	X[f]		X			X			Section 8.2.1 (core protocol). If screening laboratory assessments are performed within 3 days prior to Day 1 they do not need to be repeated
Haematology[e]	X		X	X[f]		X	X[f]		X			X			
APTT and INR	X		As clinically indicated												
TSH, free T_3 and free T_4	X		X	X		X	X		X			X			Section 8.2.1 (core protocol)

	Cycle 0 (7-day lead-in)		**C1** 28 days Weeks 1-4			**C2** 28 days Weeks 5-8			**C3 - etc** **All cycles 28 days**			**Study drug disc.** (28 days after study drug disc.)	**Safety follow-up** (90 days after study drug disc.)	**Survival follow-up**	**Notes**
Week	**1**		**1**	**4**		**5**	**8**		9, 13, 17 etc (Day 1 of each cycle)						
Day of cycle	**1**	**7**	**1**	**22**	**28**	**1**	**22**	**28**	**1**	**22[j]**	**28[j]**				
Window (days)	**0[a]**	**±2**	**±2**	**±2**	**-2**	**±2**	**±2**	**-2**	**±2**	**±2**	**-2**	**±7**	**±7**	**±7**	
Urinalysis	X		As clinically indicated												Section 8.2.1 (core protocol)
Pregnancy test	X		X			X			X			X			Section 8.2.1.2 (core protocol)
AE/SAE	X	X	X	X	X	X	X	X	X	X	X	X	X		Section 8.3 (core protocol)
Study drug administration[c,d]															
Durvalumab			X			X			X						Section 6.1
AZD6738	X Days 1-7			X Days 22-28			X Days 22-28			X Days 22-28					Section 6.1
Drug accountability	X	X	X	X	X	X	X	X	X	X	X	X			Section 6.2.4
Other administration															
Blood for [redacted] assessments[k]	X		X			X			X			X			Section 8.8 (core protocol)
Circulating soluble factors	X		X	X		X	X		X (Cycle 4 only)			X			Section 8.8 (core protocol)
Whole blood for gene expression (PAXgene RNA tubes)	X		X	X		X	X		X (Cycle 4 only)			X			Section 8.8 (core protocol)

	Cycle 0 (7-day lead-in)		**C1** 28 days Weeks 1-4			**C2** 28 days Weeks 5-8			**C3 - etc** **All cycles 28 days**			**Study drug disc.** (28 days after study drug disc.)	**Safety follow-up** (90 days after study drug disc.)	**Survival follow-up**	**Notes**
Week	**1**		**1**	**4**		**5**	**8**		9, 13, 17 etc (Day 1 of each cycle)						
Day of cycle	**1**	**7**	**1**	**22**	**28**	**1**	**22**	**28**	**1**	**22[j]**	**28[j]**				
Window (days)	**0[a]**	**±2**	**±2**	**±2**	**-2**	**±2**	**±2**	**-2**	**±2**	**±2**	**-2**	**±7**	**±7**	**±7**	
Whole blood for flow cytometry (immunophenotyping) [l]	X		X	X		X	X		X (Cycle 4 only)			X			Section 8.8 (core protocol)
TCR immuno-sequencing	X		X	X		X	X		X (Cycle 4 only)			X			Section 8.8 (core protocol)
Plasma sample for AZD6738 PK[g]	X (post-dose only)	X		X (post-dose only)	X		X (post-dose only)	X		X (post-dose, C3, C4, C8 & C12 only))	X (C3, C4, C8 & C12 only)				
Blood sample for durvalumab PK[h]			X (pre-dose and post-dose)			X (post-dose only)			X (post-dose, C4, C8 and C12 only)				X		
Blood sample for ADA for durvalumab (pre-dose except at safety follow-up)			X			X			X (C4, C8 & C12 only)				X		Section 8.5.3 (core protocol)

	Cycle 0 (7-day lead-in)		**C1** 28 days Weeks 1-4			**C2** 28 days Weeks 5-8			**C3 - etc** **All cycles 28 days**			**Study drug disc.** (28 days after study drug disc.)	**Safety follow-up** (90 days after study drug disc.)	**Survival follow-up**	**Notes**
Week	**1**		**1**	**4**		**5**	**8**		9, 13, 17 etc (Day 1 of each cycle)						
Day of cycle	**1**	**7**	**1**	**22**	**28**	**1**	**22**	**28**	**1**	**22[j]**	**28[j]**				
Window (days)	**0[a]**	**±2**	**±2**	**±2**	**-2**	**±2**	**±2**	**-2**	**±2**	**±2**	**-2**	**±7**	**±7**	**±7**	
Tumour evaluation (CT or MRI, RECIST 1.1)				Every 6 weeks ±1 week for the first 24 weeks relative to the start of combination therapy (Cycle 1 Day 1), then every 8 weeks ±1 week thereafter, until objective disease progression as defined by RECIST 1.1 and confirmed with a subsequent scan (in the absence of clinically significant deterioration)											Section 8.1 (core protocol)
Biopsy on treatment (mandatory)[m]						X									Section 8.8 (core protocol). This should align with the first RECIST assessment
Biopsy on disease progression (optional)												X			Section 8.8 (core protocol)
Subsequent cancer therapy													X	X	Section 8.1.3.1 (core protocol). To be done every 3 months
Survival status														X[i]	Section 8.1.3.1 (core protocol). To be done every 3 months

[a] Every effort should be made to minimise the time between allocation and starting treatment. Note, if main screening assessments have been performed within 3 days prior to C0D1, then assessments do not need to be performed on C0D1 pre-dose.

[b] If clinically indicated, blood pressure to be measured in the supine and standing positions after at least 10 minutes' rest.

[c] Following the final data cut-off for the module CSR (see Section 9.4.2 of the core protocol), any patients on study treatment may continue on treatment and should be assessed for safety according to standard local clinical practice. Study drug administration, SAE reporting and related safety assessment data should be recorded in the eCRF until 90 days after study drug discontinuation, when the patient will end participation in the study. The other assessments for the study will no longer be performed and those data will no longer be collected; the tumour evaluations will be performed as per standard of care. The survival follow-up will no longer be conducted.

[d] A + 2-day window is allowed for durvalumab administration; in each treatment cycle, starting with Cycle 1, AZD6738 administration will start 21 days after durvalumab infusion.

[e] Eosinophil, monocyte, lymphocyte and neutrophil counts will be recorded as part of the routine white blood cell count for safety assessment.

[f] Haematology and clinical chemistry assessments will take place on Day 22 (± 2-day window) of Cycles 1 and 2. If any toxicity is detected during these additional safety assessments, the patient will be managed as per the protocol, and as clinically indicated. In the event that a patient has an event of thrombocytopenia, anaemia and/or neutropenia that is ≥ Grade 3 during the first 2 cycles, this additional safety assessment will be included in subsequent cycles until there is no evidence of ≥ Grade 3 thrombocytopenia, anaemia and/or neutropenia for at least 2 cycles.

[g] AZD6738 PK samples: Pre-dose samples to be taken within 1 hour (± 10 minutes) before the AZD6738 dose. Post-dose samples to be taken at 1 hour (± 10 minutes) after the AZD6738 dose. On Day 7 of Cycle 0 and Day 28 (Cycle 1 onwards), samples can be taken either pre-dose and post-dose of the morning AZD6738 dose OR pre-dose and post-dose of the evening AZD6738 dose, with a -2-day window allowed (see Table 10 of core protocol Section 8.5).

[h] Durvalumab PK samples: Pre-dose sample (Cycle 1 Day 1) to be taken within 1 hour (± 10 minutes) before the start of infusion. Post-dose samples (excluding the safety follow-up sample) to be taken at the end of durvalumab infusion (or within 10 minutes from the end of infusion). (see Table 11 of core protocol Section 8.5).

[i] Ad hoc collection of survival status may be requested for overall survival analyses.

[j] After Cycle 2, Day 22 and Day 28 site visits will be performed only for cycles where an AZD6738 PK sample is to be collected (Cycles 3, 4, 8 and 12), unless a patient has an event of thrombocytopenia, anaemia and/or neutropenia that is ≥ Grade 3 during the first 2 cycles, then only the Day 22 visit will be included in subsequent cycles for haematology and clinical chemistry assessments until there is no evidence of ≥ Grade 3 thrombocytopenia, anaemia and/or neutropenia for at least 2 cycles (as described in footnote e).

[k] Whole blood to be taken every cycle for the first 3 cycles and then at every radiographic assessment visit (every 6 weeks [± 1 week] for the first 24 weeks relative to the start of combination therapy [C1D1], then every 8 weeks [± 1 week]) in all patients (at pre-dose on durvalumab dosing day) until disease progression (or study treatment discontinuation).

[l] Sample collection is for up to 60 patients only. If a flow cytometry sample is not collected at the C0D1 visit, there is no requirement to collect further samples for analysis at subsequent study visits.

[m] On-treatment biopsy is not required if a fresh tumour sample is not collected at screening.

ADA Anti-drug antibodies; AE adverse event; APTT activated partial thromboplastin time; C cycle; CD8+ cytotoxic T-cell; CSR clinical study report; CT computed tomography; CCI D day; ECG electrocardiogram; eCRF electronic Case Report Form; INR international normalised ratio; MRI magnetic resonance imaging; PD-1 programmed cell death-1; PK pharmacokinetic; Q12W every 12 weeks; Q24W every 24 weeks; RECIST 1.1 Response Evaluation Criteria in Solid Tumours 1.1; SAE serious adverse event; TCR T-cell receptor repertoire; TSH thyroid-stimulating hormone; T_3 triiodothyronine; T_4 thyroxine.

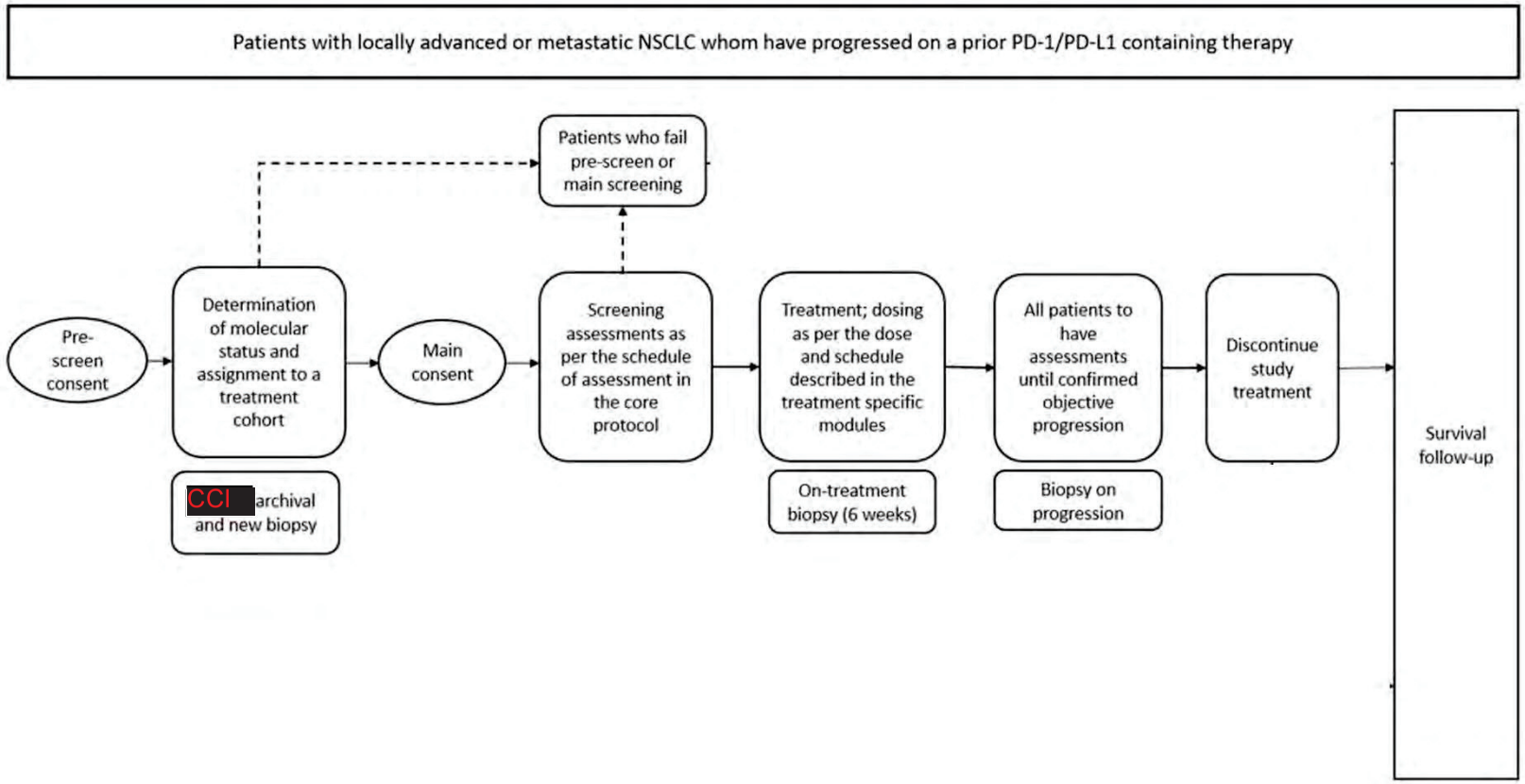
1.2 Synopsis

Please refer to Section 1.2 of the core protocol.

1.3 Schema

The general study design is summarised in Figure 1.

Figure 1 Study design



CCI NSCLC, non-small cell lung cancer; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1.

2. INTRODUCTION

Study D6185C00001 (HUDSON) is a Phase II, open-label, multi-centre umbrella study in patients who have received an anti-programmed cell death-1 (PD-1)/anti-programmed cell death-ligand 1 (PD-L1) containing therapy and a platinum-doublet regimen for locally advanced or metastatic non-small cell lung cancer (NSCLC) either separately or in combination. The patient must have had disease progression on a prior line of anti-PD-1/PD-L1 therapy. The modular design allows the evaluation of the efficacy, safety, and tolerability of multiple study drugs. This module to the core study protocol describes Module 10, which will further investigate the efficacy, safety, and tolerability of AZD6738 at doses of 160 mg twice daily (bd) and 240 mg bd, administered with durvalumab combination.

2.1 Study rationale

As described in Section 2.2 of the core protocol, immune checkpoint inhibitors targeting the PD-1/PD-L1 pathway have shown significant activity in the first- and second-line treatment settings in patients with NSCLC. However, it is becoming evident that there is a new and significant patient population emerging that does not respond to anti-PD-1/PD-L1 containing therapy (primary resistance) or progresses during anti-PD-1/PD-L1 containing therapy (acquired resistance). There is currently no established therapy for patients who have developed resistance to PD-1/PD-L1 and platinum-doublet therapies, and novel treatments for these patients are urgently needed.

The aim of this umbrella study (D6185C00001) is to investigate multiple study drugs for the treatment of NSCLC in molecularly matched and non-matched patient populations after failure of immune checkpoint inhibitors, to identify patient populations who may respond favourably to novel anti-tumour therapies.

2.2 Background

Durvalumab and AZD6738 are both currently in clinical development as anti-cancer therapies in a variety of malignancies. Durvalumab as a weight-based regimen of 10 mg/kg every 2 weeks (Q2W) has been approved for use in the treatment of patients with urothelial carcinoma (UC). On 16 February 2018, durvalumab was approved in the US for the treatment of patients with unresectable Stage III NSCLC. On 21 September 2018, durvalumab was approved in the European Union (EU) for the treatment of locally advanced, unresectable NSCLC in adults whose tumours express PD-L1 on ≥1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy. As of 12 July 2019, durvalumab is approved in over 45 countries for NSCLC. On 27 March 2020, the Food and Drug Administration approved durvalumab in combination with etoposide and either carboplatin or cisplatin as first-line treatment of patients with extensive-stage small cell lung cancer.

Module 10 will investigate both agents in combination, to test the hypothesis that the combination will result in complementary anti-tumour activity, and further investigate the optimal dose of this combination in patients with NSCLC. Brief background on AZD6738 and durvalumab, including their mechanisms of action, is provided below. For detailed descriptions of the chemistry, pharmacology, efficacy, safety and pharmacokinetics (PK) of AZD6738 and durvalumab, refer to the respective Investigator's Brochures (IBs).

The study will recruit a total of up to approximately C patients in Module 10, independent of their molecular aberration status (see Section 4.1).

2.2.1 Durvalumab

2.2.1.1 Overview of durvalumab

Expression of PD-L1 protein is an adaptive immune response that helps tumours evade detection and elimination by the immune system. PD-L1 can be induced by inflammatory signals (eg, interferon-gamma) and can be expressed on both tumour cells and tumour-associated immune cells in tumour microenvironment. PD-L1 blocks T-cell function and activation through interaction with PD-1 and CD80 (B7.1). By binding to its receptors, PD-L1 reduces cytotoxic T-cell activity, proliferation, and cytokine production. Durvalumab is a fully human, high affinity, immunoglobulin G1 kappa monoclonal antibody that selectively blocks the interaction of PD-L1 with PD-1 and cluster of differentiation (CD)80 (B7.1) while leaving PD-1/ programmed cell death ligand-2 interaction intact. Durvalumab does not induce antibody dependent cell-mediated cytotoxicity. Selective blockade of PD-L1/PD-1 and PD-L1/CD80 interactions enhances antitumour immune responses. These antitumour responses may result in tumour elimination.

Durvalumab is approved in a number of territories including the US, EU, Japan, Canada and Brazil under the brand name IMFINZI™ Injection.

The recommended dose as per the IMFINZI package insert is 10 mg/kg administered as an intravenous (IV) infusion over 60 minutes Q2W.

For more information, please refer to the latest version of the durvalumab IB.

2.2.1.2 Durvalumab data

To date, durvalumab has been given to more than CCI patients as part of ongoing studies either as monotherapy or in combination with other anticancer agents. Details on the safety profile of durvalumab monotherapy are summarised below. Refer to the current durvalumab IB for a complete summary of pre-clinical and clinical information including safety, efficacy, and PK.

Clinical activity in locally advanced NSCLC

The efficacy of durvalumab was evaluated in the PACIFIC Study, a randomised, double-blind, placebo-controlled, multicentre study in CCI patients with histologically or cytologically confirmed locally advanced, unresectable NSCLC. Patients had completed definitive platinum-based chemoradiation within 1 to 42 days prior to initiation of the study and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Ninety-three percent of patients had received a total dose of 54 to 66 Gy of radiation. The study excluded patients who had progressed following concurrent chemoradiation therapy, patients with active or prior documented autoimmune disease within 2 years of initiation of the study; a history of immunodeficiency; a history of severe immune-mediated adverse reactions; medical conditions that required systemic immunosuppression, except physiological dose of systemic corticosteroids; active tuberculosis or hepatitis B or C or HIV infection or patients receiving live attenuated vaccine within 30 days before or after the start of durvalumab. Patients were randomised 2:1 to receive 10 mg/kg durvalumab (n=476) or 10 mg/kg placebo (n=237) via IV infusion Q2W for up to 12 months or until unacceptable toxicity or confirmed disease progression. Randomisation was stratified by gender, age (<65 years vs. ≥65 years) and smoking status (smoker vs. nonsmoker). Patients with disease control at 12 months were given the option to be re-treated upon disease progression. Tumour assessments were conducted every 8 weeks for the first 12 months and then every 12 weeks thereafter.

The demographics and baseline disease characteristics were well balanced between study arms. Baseline demographics of the overall study population were as follows: male (70%), age ≥65 years (45%), White (69%), Asian (27%), other (4%), current smoker (16%), past-smoker (75%), and never smoker (9%), World Health Organisation (WHO)/ECOG PS 0 (49%), WHO/ECOG PS 1 (50%). Disease characteristics were as follows: Stage IIIA (54%), Stage IIIB (44%), histological subgroups of squamous (47%), non-squamous (53%), PD-L1 expression in tumour cells (TC)≥25% (22%), PD-L1 expression TC<25% (41%). (PD-L1 status was retrospectively analysed using the Ventana PD-L1 [SP263] Assay in 451 patients with available samples, taken prior to concurrent chemoradiation therapy).

At the time of the interim progression-free survival (PFS) analysis, the median PFS by blinded independent central review (BICR) was significantly longer with durvalumab treatment (16.8 months) compared with placebo (5.6 months); hazard ratio 0.52; 98.9% CI: 0.39, 0.70; p<0.0001. At the time of the interim overall survival (OS) analysis, the median OS was not reached for the durvalumab arm and was 29.1 months for the placebo arm; hazard ratio, 0.69; 95% CI, 0.55, 0.86). The 36-month OS rate was 57.0% with durvalumab vs 43.5% with placebo.

Clinical activity in recurrent and metastatic NSCLC

Based on current data from the Study CD-ON-MEDI4736-1108 (NCT01693562), evidence of clinical activity with durvalumab has been observed. The following responses were observed in patients with NSCLC.

Overall, clinical activity was observed in both the PD-L1 high (defined as having tumour cells [TC] ≥25%) and PD-L1 low/negative (defined as TC <25%) subgroups, however, patients with PD-L1 high tumours had higher objective response rates (ORRs).

The ORR per BICR was 21.8% and 6.4% in patients with PD-L1 high and low/negative tumours, respectively and 15.3% in the overall population regardless of PD-L1 expression. The ORR was 25.9%, 14.3% and, 11.5% in the 1L, 2L and 3L+ cohorts, respectively. Median duration of response (DOR) was 17.74 months. Median OS was 12.4 months; median OS was 21.0, 11.8 and 9.3 months in the 1L, 2L and 3L+ cohorts, respectively. The OS rate at 24 months was 29.6% (Antonia et al 2019).

The ATLANTIC study in third-line or higher NSCLC showed higher ORR and survival outcomes in high PD-L1 positive patients. Across cohorts the ORR ranged from 3 to 43%, median progression-free survival (PFS) ranged from 1.8 to 5.5 months and median OS ranged from 5.9 to 13.6 months but was not reached at the time of initial reporting in the >90% PD-L1 expressors. The ORR and survival outcomes reported in durvalumab studies are in keeping with other similar agents targeting the PD-1/PD-L1 axis (Garassino et al 2017).

Preliminary efficacy data from the MYSTIC study in first-line advanced or metastatic NSCLC showed that in PD-L1 high (≥25% TC) NSCLC, median PFS by BICR was 4.7 months for durvalumab monotherapy and 5.4 months for chemotherapy; hazard ratio of 0.87; 99.5% CI: 0.593, 1.285; p=0.324. The median OS was 16.3 months for the durvalumab arm and 12.9 months for the chemotherapy arm; hazard ratio for death was 0.76; 97.54% CI: 0.564, 1.019; p=0.036. The 24-month OS rate was 38.3% vs 22.7% and the 12-month PFS rate was 32.3% vs 14.3% for the durvalumab and chemotherapy arms respectively. When durvalumab was administered in combination with tremelimumab, the median PFS by BICR was 3.9 months for durvalumab + tremelimumab and 5.4 months for chemotherapy; hazard ratio of 1.05; 99.5% CI: 0.722, 1.534; p=0.705. The median OS was 11.9 months for the durvalumab + tremelimumab arm and 12.9 months for the chemotherapy arm; hazard ratio for death was 0.85; 98.77% CI: 0.611, 1.173; p=0.202. The 24-month OS rate was 35.4% vs 22.7% and the 12-month PFS rate was 25.8% vs 14.3% for the durvalumab + tremelimumab and chemotherapy arms respectively (Rizvi et al 2020).

Immuno-oncology agents targeting the PD-1/PD-L1 pathway have demonstrated activity as monotherapy and in combination with chemotherapy in patients who are immunotherapy-naïve. However, the present study will recruit patients who either have

primary resistance to anti-PD-1/PD-L1 therapy or who developed acquired resistance while on anti-PD-1/PD-L1 therapy. Thus, in this immunotherapy-resistant setting, durvalumab will be administered in combination with an agent that has a different and complementary mechanism of action in order to maximise the likelihood of clinical activity.

2.2.2 AZD6738

2.2.2.1 Overview of AZD6738

AZD6738 is a potent, selective inhibitor of ataxia telangiectasia and Rad3-related protein (ATR), with good selectivity against other phosphatidylinositol 3-kinase-related kinase (PIKK) family members. This compound is being developed as an oral anti-tumour agent as monotherapy or in combination with the checkpoint inhibitor durvalumab (anti-PD-L1), polyadenosine 5'diphosphoribose (poly [ADP ribose]) polymerisation (PARP) inhibitors, or DNA-damaging radiotherapy or chemotherapy, in patients with DNA damage response (DDR)-deficient tumours.

ATR is a serine/threonine protein kinase and member of the PIKK family. During normal DNA replication, ATR is activated by persistent single strand DNA breaks (SSBs) that occur if a replication fork is stalled in S-phase during DNA synthesis. Activation of ATR triggers a signal cascade leading to cell cycle arrest in S-phase whilst the DNA is repaired and the stalled replication fork resolved. Without repair, SSBs can progress to double strand DNA breaks (DSBs), the most genotoxic form of DNA damage due to the consequences DSBs have for accurate chromosome segregation during cell division (O'Connor 2015). ATR is also recruited to single-strand DNA coated with Replication Protein A following single-strand DNA damage or the resection of DSBs.

AZD6738 is an inhibitor of ATR that blocks this activity, causing stalled replication forks to collapse leading to DSBs and a dependence on ATM, a key enzyme coordinating the cellular response to DSBs (Weber and Ryan 2015). If the level of DNA damage exceeds the capacity to repair, nuclear fragmentation and entry into programmed cell death (apoptosis) occur (Antonia et al 2019; Cimprich and Cortez 2008).

ATM is a closely related kinase that is recruited to DSBs and like ATR, has both checkpoint and repair functions. In normal cells, there is a significant interplay between ATR and ATM as stalled replication forks can be converted into DSBs through further DNA damage and the resection of DSBs generates single-stranded DNA (Stewart et al 2015; Toledo et al 2011). During tumourigenesis, ATM can be inactivated or lost providing a selection advantage for the tumour cell through the increased potential for genome alteration, and an increased dependence on ATR function. Similarly, oncogene activation such as through aberrant Myc, RAS, or cyclin D/E activity, or through tumour suppressor loss such as inactivation of ARID1A or RNA splicing factors (transcription replication collisions) may lead to high levels of replication stress, an accumulation of stalled replication forks, and a dependence on ATR

function for cancer cell survival (Forment and O'Connor 2018; Nguyen et al 2018; Williamson et al 2016).

Preclinically, AZD6738 has demonstrated antitumour activity in gastric cancer cells. In SNU-601 cells with dysfunctional ATM, AZD6738 treatment led to an accumulation of DNA damage due to dysfunctional *RAD51* foci formation, S-phase arrest, and caspase 3-dependent apoptosis, whereas SNU-484 cells with functional ATM were not sensitive to AZD6738. In addition, in an in vivo tumour xenograft mouse model, AZD6738 significantly suppressed tumour growth and increased apoptosis. These findings suggest synthetic lethality between ATR inhibition and ATM deficiency in gastric cancer cells (Min et al 2017).

2.2.2.2 AZD6738 data

Currently, for the ATR programme, there are a number of ongoing AstraZeneca sponsored clinical studies with AZD6738 in addition to HUDSON, where combinations of AZD6738 with carboplatin, olaparib or durvalumab are being explored.

In addition, Study D533BC00001 (LATIFY, NCT05450692) will use AZD6738 plus durvalumab versus standard of care docetaxel in patients with NSCLC whose disease has progressed on or after prior anti-PD-(L)1 therapy and platinum-based chemotherapy.

A number of AstraZeneca sponsored studies incorporating AZD6738 are ongoing or completed:

- D419QC00002 study (BALTIC, NCT02937818), using AZD6738 and olaparib combination in patients with platinum refractory extensive-stage small-cell lung cancer, has completed with 21 patients dosed.
- D5336C00001 (VIOLETTE study, NCT03330847), using the AZD6738 and olaparib combination in patients with triple negative breast cancer with BRCA mutation (stratum A), HRR mutation (stratum B) and non-HRR mutation (stratum C), has completed and 109 patients were treated with AZD6738.
- Based on primary analysis of the D5336C00001 study, D6018C00004 (DUETTE, NCT04239014), using the combination of AZD6738 and olaparib as second maintenance treatment in patients with platinum-sensitive relapsed epithelial ovarian cancer, who have previously received PARP inhibitor maintenance treatment, was terminated (no patients were randomised to treatment).
- A previous Phase I study (D5330C00001; NCT01955668) to assess multiple ascending doses of AZD6738 in patients with prospectively identified 11q-deleted relapsed/refractory chronic lymphocytic leukaemia (CLL), prolymphocytic leukaemia (PLL) or B-cell lymphomas was stopped after one patient was treated, due to difficulties in recruitment.
- An AstraZeneca sponsored study (D5330C00008, NCT03328273) tested AZD6738 in combination with acalabrutinib in patients with relapsed/refractory CLL; the monotherapy part of the study was discontinued due to CCI suggesting that

patients had CCI [redacted] with AZD6738 monotherapy, and the study was subsequently terminated early because of operational challenges impacting study execution.

- The platform study for the treatment of relapsed or refractory aggressive non-Hodgkin's lymphoma (Study D9820C00001; PRISM) recruited 2 patients in a treatment module including AZD6738 and acalabrutinib.
- Study D533AC00001 (MONETTE) is using AZD6738 as monotherapy and in combination with durvalumab in patients with unresectable or advanced melanoma who have progressed during treatment with a PD-(L)1 inhibitor ± cytotoxic T-lymphocyte associated protein 4 (CTLA-4) inhibitor.

In addition, there are Externally Sponsored Research (ESR) studies ongoing where AZD6738 is being investigated in combination with olaparib in ovarian cancer (CAPRI study [D5334C00001; NCT03462342]; results from Cohort B have been published [Shah et al 2021]) and in BAF250a (ARID1A)-deficient or BAF250a-expressing advanced solid cancers (D5330C00012; NCT03682289). Completed ERS studies include studies where AZD6738 was investigated as a single agent or in combination with radiotherapy (PATRIOT study [D5330C00002; NCT02223923]), in combination with paclitaxel (Pre-VIKTORY study [D5330C00006; NCT02630199] in patients with advanced solid tumours and enriched with metastatic melanoma [Kim et al 2021]), in combination with durvalumab (VIKTORY study [D6183C00003; NCT02299648] in patients with metastatic melanoma and gastric cancer [Lee et al 2021]), or in combination with olaparib in patients with solid tumours harbouring mutations in homology-directed repair genes (OLAPCO [D0810C00090; NCT02576444]; [Mahdi et al 2021]), in patients with relapsed small cell lung cancer (SUKSES-N2 [D5334C00003; NCT03428607]), and in triple-negative breast cancer (PlasmaMATCH Cohort E [D6184C00001; NCT03182634]).

Anaemia, thrombocytopenia, and neutropenia (including febrile neutropenia), CCI [redacted] have been reported when AZD6738 is used as monotherapy and when used in combination with olaparib and durvalumab.

In general, a higher incidence of haematological toxicities was seen when AZD6738 was used at higher doses, longer schedules, or in combination with myelosuppressive agents. Similarly, the incidence of haematological toxicity was comparatively higher when AZD6738 was administered in patients with haematological malignancies.

Adverse events reported in clinical studies were predictable from pre-clinical data and from what is known about the mechanism of action of AZD6738, the combination drugs given, and/or the underlying disease. The observed toxicities in the clinical setting have been manageable with current clinical practice.

See the current IB for further information.

The non-clinical and emerging safety profile has not identified any risks that would preclude investigation of AZD6738 in the advanced cancer setting. Based on the identified and potential risks associated with treatment, this protocol incorporates mandatory safety monitoring procedures and additional guidance documents to assist with early diagnosis and rapid management of potential drug-related symptoms.

2.2.3 Durvalumab and AZD6738 in combination

The underpinning hypothesis for combining durvalumab and AZD6738 is that the combination will result in induction of immune memory, leading to more durable control of tumour growth than is achievable with either modality alone. Molecularly targeted therapies may serve as "cancer vaccines" inducing the killing of tumour cells and resulting in the release of tumour antigens and neoantigens, which can then be presented by antigen presenting cells (APCs) to tumour-specific T-cells. These T-cells become activated but also upregulate inhibitory checkpoints such as CTLA-4 and PD-1, which can be blocked with antibodies to permit enhanced anti-tumour T-cell responses, including memory T-cell responses, to enable long-term control of disease and possible cure. In addition, the use of targeted agents to directly kill tumour cells, with release of tumour antigens, may focus the activated immune response generated by immunotherapy agents on tumour antigens rather than self-antigens expressed on normal tissues, resulting in fewer adverse events (AEs).

Based on our current understanding of the immune response, one can identify 3 distinct steps that must be achieved in order to mount effective anti-tumour immunity (Mellman et al 2011):

1 To initiate immunity, dendritic cells must sample antigens derived from the tumour, mature and differentiate, and ultimately process and present tumour antigens
2 Next, in lymphoid organs, tumour antigen-loaded dendritic cells must generate protective T-cell responses
3 Finally, cancer specific T-cells must enter the tumour bed to perform their function. To do so, they have to overcome the challenge of stromal immune suppression

Single agent PD-1/PD-L1 axis inhibitors primarily impact this third step: relieving stromal suppression. ATR inhibition causes an increase in S-phase DNA damage in tumour cells that is expected to lead to the accumulation of unincorporated DNA fragments in the cytosol, activating the stimulator of interferon genes (STING)/tank binding kinase-1 (TBK1)/interferon regulatory factor-3 (IRF3) innate immune response (Parkes et al 2017). If sufficient DNA damage accumulates, tumour cell death is expected to release tumour specific antigens, changing the tumour microenvironment to promoting antigen presentation (Galluzzi et al 2012). Either consequence of ATR inhibition has the potential to prime the immune response, as outlined in Step 1 above.

Clinical experience of the combination of AZD6738 and durvalumab is summarised in the IB for AZD6738.

The recommended Phase 2 dose was ascertained from Study D5330C00004 Module 3, in which the following doses were studied:

- Cohort 1 AZD6738 80 mg twice daily (bd) Cycle 0 Days 1 to 14, Cycle 1 Days 22 to 28
- Cohort 2 AZD6738 160 mg bd Cycle 0 Days 1 to 14, Cycle 1 Days 22 to 28
- Cohort 3 AZD6738 320 mg once daily (od) Cycle 0 Days 1 to 14, Cycle 1 Days 22 to 28
- Cohort 4 AZD6738 320 mg od Cycle 0 Days 1 to 14, Cycle 1 Days 15 to 28
- Cohort 5 AZD6738 240 mg bd Cycle 0 Days 1 to 7, Cycle 1 Days 22 to 28
- Cohort 6 AZD6738 240 mg bd Cycle 0 Days 1 to 14, Cycle 1 Days 15 to 28.

AZD6738 240 mg bd Cycle 0 Days 1 to 14, Cycle 1 Days 15 to 28 combined with durvalumab 1500 mg on Day 1 q28 was declared as the recommended Phase II dose.

No reproductive toxicology or teratogenic studies have been conducted with AZD6738 to date, and it is unknown whether the drug is excreted in human milk. Therefore, women of childbearing potential and men should agree to use adequate contraception prior to study entry and for the duration of study participation, and women who are breast feeding are excluded from the study. Both women and men should be fully informed of the lack of reproductive toxicity testing, and women must have a negative pregnancy test prior to enrolment.

This study will investigate whether the combined effects of AZD6738 and durvalumab can overcome the immune-resistance that has been developed clinically in patients treated with prior PD-1/PD-L1 containing therapy. Clinical responses to AZD6738 in combination with durvalumab have been observed in patients with NSCLC and HNSCC in Study D5330C00004 with tumours that have been characterised as PD-L1 expression low/negative. In total, as assessed by RECIST 1.1, there have been three confirmed partial responses (two NSCLC patients and one squamous cell carcinoma of the head and neck [SCCHN]), one unconfirmed response (NSCLC) and one confirmed complete response in a NSCLC patient. In addition, 12 cases of stable disease have been seen (unclean data, data cut-off 13 June 2018). Accordingly, it is expected that if loss of PD-L1 expression is involved in generation of resistance to front-line PD-1/PD-L1 axis inhibitors that the combination with AZD6738, by removing the dependence on PD-L1 expression, will restore sensitivity.

2.3 Benefit/risk assessment

As described in Section 2.3 of the core protocol, patients recruited to this study are not expected to have other treatment options apart from monotherapy chemotherapy, such as docetaxel. The survival outcome and toxicity profile of chemotherapy in this setting mean that other active therapies are highly desirable and present a potential advantage for patients.

The study design aims to identify patient populations who may respond favourably to novel anti-tumour therapies. Based upon the available non-clinical and clinical safety data, the limited survival benefit provided by the currently available treatment options to patients, the limited life expectancy due to malignant disease, and the hypothesis of the complementary effect of the 2 agents, the investigation of the potential therapeutic efficacy of the combination of durvalumab with AZD6738 in patients with advanced or metastatic NSCLC is acceptable, and the overall benefit/risk assessment supports the proposed study design. Exploration of the AZD6738 160 mg bd dose is part of the overall aim to determine the optimal benefit/risk for AZD6738.

3. OBJECTIVES AND ENDPOINTS

Please refer to the core protocol.

4. STUDY DESIGN

4.1 Overall design

This is an open-label, multi-centre, umbrella study in patients who have received an anti-PD-1/PD-L1 containing therapy and a platinum-doublet regimen for locally advanced or metastatic NSCLC either separately or in combination. The patient must have had disease progression on a prior line of anti-PD-1/PD-L1 therapy. For an overview of the study design see Figure 1; further details on the overall design are provided in Section 4 of the core protocol. For details on the study treatments given in Module 10, see Section 6.1.

Module 10 will further evaluate the efficacy, safety, and tolerability of durvalumab (given IV) in combination with 2 different dose regimens of AZD6738 (given orally) in 2 cohorts of patients, independent of their molecular aberration status. Up to approximately 80 patients (up to approximately 40 patients in each cohort) will be randomly allocated in a 2:1 ratio via the study interactive response technology (IRT) system to receive one of the following doses of AZD6738 in combination with durvalumab:

- **Cohort C.10.160:** AZD6738 160 mg bd
- **Cohort C.10.240:** AZD6738 240 mg bd

Patients will be defined by prior response to immunotherapy; primary resistance or acquired resistance. These terms are defined as follows:

- Primary resistance; patients who had anti-PD-1/PD-L1 containing therapy but had progression of disease (PD) within ≤24 weeks from the start of treatment.
- Acquired resistance; patients who had progressive disease >24 weeks from the start of anti-PD-1/PD-L1 containing therapy whilst still on that treatment.

For the patient allocation process, see Section 4.1.4 (Clinical Screening Procedures) of the core CSP. Details of the Module 10 allocation procedure are described in Section 6.3 and in the study IRT documents.

A study flow diagram is provided in the core protocol (Figure 4).

4.2 Scientific rationale for study design

The study aims to identify patient populations who may respond favourably to novel anti-tumour therapies, and the modular design allows evaluation of the efficacy, safety, and tolerability of multiple study drugs. The study requires an open-label design owing to the different schedules and routes of administration of the study drugs.

Module 10 will enrol patients, independent of their molecular aberration status, in order to further investigate the optimal dose of AZD6738 in combination with durvalumab. Introduction of Module 10 follows regulatory recommendation to gather additional data on the impact of different doses of AZD6738 to support a registration-based Phase 3 study and as such, the study decision framework does not apply.

4.3 Justification for dose

4.3.1 Justification for durvalumab dose

A durvalumab dose of 20 mg/kg every 4 weeks (Q4W) is supported by in vitro data, pre-clinical activity, clinical PK/pharmacodynamics, biomarkers, and activity data from Study CD-ON-MEDI4736-1108 (hereafter referred to as Study 1108) in patients with advanced solid tumours and from a Phase I study performed in Japanese patients with advanced solid tumours (D4190C00002).

Please refer to the current durvalumab IB for further updates on data from ongoing studies.

PK/Pharmacodynamic data

Based on available PK/pharmacodynamic data from ongoing Study 1108 with doses ranging from 0.1 to 10 mg/kg Q4W or 15 mg/kg Q4W, durvalumab exhibited non-linear (dose dependent) PK consistent with target-mediated drug disposition. The PK approached linearity at ≥3 mg/kg Q4W, suggesting near complete target saturation (membrane-bound and sPD-L1), and further shows that the durvalumab dosing frequency can be adapted to a particular regimen given the linearity seen at doses higher than 3 mg/kg. The expected half-life with doses ≥3 mg/kg Q4W is approximately 21 days. A dose-dependent suppression in peripheral sPD-L1 was observed over the dose range studied, consistent with engagement of durvalumab with PD-L1. A low level of immunogenicity has been observed. No patients have experienced immune-complex disease following exposure to durvalumab. (For further information on immunogenicity, please see the current durvalumab IB).

A population PK model was developed using the data from Study 1108 (doses=0.1 to 10 mg/kg Q2W or 15 mg/kg Q4W; Fairman et al 2014). Multiple simulations indicate that a similar overall exposure is expected following both 10 mg/kg Q4W and 20 mg/kg Q4W regimens, as represented by AUC_{ss} (4 weeks). Median $C_{max,ss}$ is expected to be higher with 20 mg/kg Q4W (~1.5 fold) and median $C_{trough,ss}$ is expected to be higher with 10 mg/kg Q4W (~1.25-fold). Clinical activity with the 20 mg/kg Q4W dosing regimen is anticipated to be consistent with 10 mg/kg Q4W with the proposed similar dose of 20 mg/kg Q4W expected to (a) achieve complete target saturation in majority of patients; (b) account for anticipated variability in PK, pharmacodynamics, and clinical activity in diverse cancer populations; (c) maintain sufficient PK exposure in case of ADA impact; and (d) achieve PK exposure that yielded maximal antitumor activity in animal models.

Given the similar area under the serum drug concentration-time curve (AUC) and modest differences in median peak and trough levels at steady state, the observation that both regimens maintain complete sPD-L1 suppression at trough, and the available clinical data, the 20 mg/kg Q4W and 10 mg/kg Q4W regimens are expected to have similar efficacy and safety profiles, supporting further development with a dose of 20 mg/kg Q4W.

Clinical data

Refer to the current durvalumab IB for a complete summary of clinical information including safety, efficacy, and PK at the 20 mg/kg Q4W regimen.

Rationale for fixed dosing

A population PK model was developed for durvalumab using monotherapy data Study 1108 (CCI doses=0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W; solid tumours). Population PK analysis indicated only minor impact of body weight on the PK of durvalumab (coefficient of ≤0.5). The impact of body weight-based (10 mg/kg Q2W) and fixed dosing (750 mg Q2W) of durvalumab was evaluated by comparing predicted steady state PK concentrations (5th, median, and 95th percentiles) using the population PK model. A fixed dose of 750 mg was selected to approximate 10 mg/kg (based on median body weight of ~75 kg). A total of 1000 patients were simulated using body weight distribution of 40 to 120 kg. Simulation results demonstrate that body weight-based and fixed dosing regimens yield similar median steady state PK concentrations with slightly less overall between-patient variability with fixed dosing regimen.

Similar findings have been reported by others (Narwal et al 2013, Ng et al 2006, Wang et al 2009, Zhang et al 2012). Wang and colleagues investigated 12 monoclonal antibodies and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies (Wang et al 2009). In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-patient variability in PK/pharmacodynamic parameters (Zhang et al 2012).

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar PK exposure and variability, AstraZeneca considered it feasible to switch to fixed dosing regimens. Based on average body weight of 75 kg, a fixed dose of 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) is included in the current study.

An exception to 1500 mg fixed dosing is made for patients with low body weight (below 30 kg). Patients with a body weight of 30 kg or less must receive weight-based dosing, equivalent to 20 mg/kg, until weight increases to greater than 30 kg. At this time, fixed dosing data for patients weighing below 30 kg (corresponding to doses greater than 50 mg/kg) are not available and are not yet supported by product development.

Thus, the clinical activity observed coupled with the safety profile, translational science correlates, and non-clinical data supports further development with a dose of 1500 mg Q4W. The durvalumab dose will not be modified during the study.

4.3.2 Justification for AZD6738 dose

This study will further investigate the optimal dose of the AZD6738 and durvalumab combination to evaluate if the lower dose of 160 mg bd provides a different risk/benefit analysis compared to 240 mg bd, given exposure between each dose level is likely to overlap. This is based on the dose of AZD6738 obtained from Module 3 of the dose escalation and expansion cohort of Study D5330C00004 where a total of C patients have been treated (data cut-off 21 February 2022) and doses of AZD6738 from 80 mg up to 240 mg bd were CCI . Days CCI is based on clinical safety and tolerability (mainly CCI safety outcomes). In addition, population PK model simulations showed that the dose of 240 mg bd for C days is predicted to CCI the percentage of patients CCI having an optimal cycle cover, defined as the time in which plasma concentrations of AZD6738 are maintained above the in vitro IC_{90} per cycle, of CCI hours. The target of CCI hours is based on preclinical data and is considered optimal to achieve CCI tumour regression under AZD6738 monotherapy. A 160 mg bd × 7-day dosing is predicted to CCI the optimal cover over IC_{90} per cycle in CCI of patients compared to 240 mg bd × 7-day dosing. In addition, CCI AZD6738 dosing maximises T-cell proliferative burst during the 3-week off period, potentially promoting upregulation of PD-L1 which can be subsequently blocked with durvalumab to enhance anti-tumour T-cell responses. T-cell proliferation is CCI to change between the 160 mg and 240 mg doses given the regimen will be unchanged.

Considering emerging PK data from ongoing studies, there is CCI

Please refer to the AZD6738 Investigational Medicinal Product Dossier for further information about the dose selection and to the AZD6738 IB for further information around the in vitro threshold values.

4.4 End of study definition

Please refer to the core protocol.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study in order to be assigned to a study cohort. Under no circumstances can there be exceptions to this rule. Patients who do not meet the entry requirements are screen failures; refer to Section 5.4 of the core protocol.

5.1 Inclusion criteria (Module 10-specific)

Patients are eligible to be included in the study only if all the following inclusion criteria apply. Please also refer to the Section 5.1 of the core protocol for the inclusion criteria applicable to all modules in the study. Additional inclusion criteria applicable to Module 10 only are described in this section.

R-1 Patients must fulfil all the core eligibility criteria.

5.2 Exclusion criteria (Module 10-specific)

Patients must not enter Module 10 of the study if any of the following exclusion criteria apply. Refer to Section 5.2 of the core protocol for the exclusion criteria applicable to all modules in the study. Additional exclusion criteria applicable to Module 10 only are described below:

Medical conditions

New exclusion criterion added in CSP version 11.0:

R-1 Patients whose tumour samples have known targetable alterations in EGFR and/or ALK, ROS1, BRAF, MET or RET at initial diagnosis are excluded. In addition, patients whose tumour samples are identified to have targetable alterations in EGFR, ALK, ROS1, BRAF, MET or RET prior to study enrolment will need the investigator to confirm interest in enrolling the patient in the study with the sponsor. If targeted alterations are detected retrospectively in central test results, the investigator should assess benefit of ongoing treatment (as specified in the core protocol, Section 7.3).

R-2 Diagnosis of ataxia telangiectasia.

R-3 Refractory nausea and vomiting, chronic gastrointestinal diseases or previous significant bowel resection, with clinically significant sequelae that would preclude adequate absorption of AZD6738.

R-4 Inadequate bone marrow reserve or organ function as demonstrated by any of the following laboratory values: absolute neutrophil count <1.5 x 10^9/L; platelet count <100 x 10^9/L; haemoglobin <90 g/L, with no blood transfusion (packed red blood cells) in the past 28 days.

R-5 Persisting (>4 weeks) severe pancytopenia due to previous therapy rather than disease (absolute neutrophil count [ANC] <0.5 x 10^9/L or platelets <50 x 10^9/L).

R-6 Creatinine clearance <40 mL/min calculated by Cockcroft-Gault equation (see Table 5 in the core protocol for the calculation).

R-7 Haematuria: +++ on microscopy or dipstick.

R-8 INR ≥1.5 or other evidence of impaired hepatic synthesis function.

R-9 Alkaline phosphatase (ALP) >2.5 x upper limit of normal (ULN) (and liver disease unrelated to the tumour). Patients with elevated ALP due to tumour related bone metastases or liver metastases will be eligible.

R-10 Patients with relative hypotension (<100/60 mmHg) or clinically relevant orthostatic hypotension, including a fall in blood pressure of >20 mmHg.

Prior/concomitant therapy

R-11 Receiving, or having received, concomitant medications, herbal supplements and/or foods that significantly modulate cytochrome P450 3A4 (CYP3A4) or P-glycoprotein (P-gp) activity (washout periods of 2 weeks, but 3 weeks for St. John's Wort). Note these include common azole antifungals, macrolide antibiotics and other medications.

R-12 Prior exposure to an ATR inhibitor.

Other

R-13 Inability to swallow the formulated product.

For procedures for withdrawal of incorrectly enrolled patients see Section 7.3 of the core protocol.

5.3 Lifestyle restrictions

5.3.1 Restrictions applicable to durvalumab

Patients should not donate blood or blood components while participating in this study and through 90 days after receipt of the final dose of durvalumab or until alternate anticancer therapy is started.

Immunosuppressive medications including, but not limited to systemic corticosteroids at doses beyond 10 mg/day of prednisone or equivalent, methotrexate, azathioprine and tumour necrosis factor alpha blockers are prohibited. Use of immunosuppressive medications for the management of study drug-related AEs and in patients with contrast allergies is acceptable. In addition, use of topical, inhaled and intranasal corticosteroids is permitted (see Table 4).

Live attenuated vaccines within 30 days of durvalumab dosing are prohibited (ie, 30 days prior to the first dose, during treatment with durvalumab and for 180 days post-discontinuation of durvalumab) (see Table 4). Inactivated viruses, such as those in the influenza vaccine or authorised and approved Coronavirus Disease 2019 (COVID-19) vaccines, are permitted (see Table 5).

5.3.2 Restrictions applicable to AZD6738

Please refer to section 5.3 of the core protocol for contraception requirements.

5.4 Screen failures

Please refer to the core protocol.

6. STUDY TREATMENTS

Study treatment is defined as any study drug(s) (including marketed product comparator and placebo) or medical device(s) intended to be administered to a study participant according to the study protocol. Study treatment in Module 10 refers to durvalumab and AZD6738.

6.1 Treatments administered

6.1.1 Study drugs

Table 2 Study drugs

	AZD6738	Durvalumab
Dosage formulation:	Oral tablets in either 20, 80 or 100 mg	Supplied as a vialed liquid solution containing 500 mg (nominal) durvalumab per vial. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine hydrochloride, 275 mM trehalose dihydrate, 0.02% (w/v) polysorbate 80, at pH 6.0. The nominal fill volume is 10.0 mL.
Route of administration:	Oral	IV infusion
Dosing instructions:	160 mg or 240 mg twice daily in Cycle 0 Days 1-7, followed by 7 days on treatment in each cycle between Days 22 and 28.	Patients enrolled in the study will receive 1500 mg via IV infusion Q4W + 2 days (fixed dosing for patients >30 kg body weight).

Table 2 Study drugs

	AZD6738	Durvalumab
Packaging and labelling	Study drug will be provided in high-density polyethylene bottles with child-resistant closures. Labels will be prepared in accordance with GMP and local regulatory guidelines. Label text will be translated into local language, as required. AZD6738 will be provided with either single-panel labels or multi-language booklet labels. Specific dosing instructions will not be included on the label; the site must complete the "Patient Dispensing Card" with the details of the dosing instructions at the time of dispensing. The investigator's emergency contact details will not be on the label, but can be found in the informed consent and the 'Patient Dispensing Card'. For emergency purposes the patient must be in possession of the emergency contact details at all times.	Study drug will be provided in vials. Each vial will be labelled in accordance with GMP and per country regulatory requirement. Labels will be prepared in accordance with GMP and local regulatory guidelines. Label text will be translated into local language, as required. Durvalumab will be provided with either single-panel labels or multi-language booklet labels. The investigator's emergency contact details will not be on the label, but can be found in the informed consent and the 'Patient Emergency Card'. For emergency purposes the patient must be in possession of the emergency contact details at all times.
Provider	AstraZeneca	AstraZeneca. Commercially available 0.9% (w/v) saline or 5% (w/v) dextrose IV bags will be supplied by each site.

bd twice daily; GMP Good Manufacturing Practice; IV intravenous(ly); Q4W every 4 weeks; w/v weight/volume

6.2 Preparation/handling/storage/accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study drugs received and any discrepancies are reported and resolved before use of the study drug.

Only patients enrolled in the study may receive study drugs and only authorised site staff may supply or administer study drugs. All study drugs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study drugs accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study drug are provided in the Pharmacy Manual.

6.2.1 Durvalumab preparation and handling

Durvalumab will be supplied by AstraZeneca as a 500 mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine hydrochloride, 275 mM trehalose dihydrate, and 0.02% (weight/volume [w/v]) polysorbate 80; it has a pH of 6.0 and a density of 1.054 g/mL. The nominal fill volume is 10.0 mL.

Study drug vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. The vials should be kept in the original packaging until use to prevent prolonged light exposure.

The dose of durvalumab for administration must be prepared by the investigator's or site's designated study drug manager using aseptic technique. Total time from needle puncture of the durvalumab vial to the start of administration should not exceed 4 hours at room temperature or 24 hours at 2°C to 8°C (36°F to 46°F). If the final product is stored at both refrigerated and ambient temperatures, the total time should not exceed 24 hours.

A dose of 1500 mg (for patients >30 kg body weight) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab concentration ranging from 1 to 15 mg/mL and delivered through an IV-administration set with a 0.2-µm or 0.22-µm filter. Add 30.0 mL (ie, 1500 mg) of durvalumab to an appropriately sized IV bag such that the final concentration is within 1 to 15 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

If a patient's body weight falls ≤30 kg during the study, (s)he will be withdrawn from the study treatment unless (s)he derives some clinical benefit according to the treating physician. In this case, and following agreement between the treating physician and the sponsor, the patient may continue treatment at a body-weight adapted dose of 20 mg/kg actual body weight.

Weight-based dosing at 20 mg/kg (for patients ≤30 kg) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab concentration ranging from 1 to 15 mg/mL, and delivered through an IV administration set with a 0.2-µm or 0.22-µm filter. An example of a weight-based dose calculation is shown in Section 6.2.1.1.

Standard infusion time is one hour (±15 minutes), however if there are interruptions during infusion, the total allowed infusion time should not exceed 8 hours at room temperature.

If either preparation time or infusion time exceeds the time limits a new dose must be prepared from new vials. Durvalumab does not contain preservatives, and any unused portion must be discarded.

Do not co-administer other drugs through the same infusion line.

The IV line will be flushed with a volume of IV diluent equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered.

Patients will be monitored before, during, and after the first durvalumab infusion with assessment of vital signs at the times specified in the SoA (Table 1) and Section 8.2.3 of the core protocol. If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be at the investigator's discretion (suggested 30 minutes after each durvalumab infusion). For management of patients who experience an infusion reaction, please refer to the toxicity and management guidelines for infusion-related reactions.

Durvalumab (1500 mg) will be administered via IV infusion Q4W + 2 days. Treatment with durvalumab will commence on Day 1 following confirmation of eligibility and will continue on a Q4W schedule until disease progression is confirmed.

6.2.1.1 Durvalumab weight-based calculation

If a patient's body weight falls ≤30 kg during the study, (s)he will be withdrawn from the study treatment unless (s)he derives some clinical benefit according to the treating physician. In this case, and following agreement between the treating physician and the sponsor, the patient may continue treatment at a body-weight adapted dose of 20 mg/kg of durvalumab Q4W until the weight improves to >30 kg, at which point the patient should start receiving the fixed dosing of durvalumab 1500 mg Q4W:

1 Cohort dose: X mg/kg

2 Patient weight: Y kg

3 Dose for patient: XY mg = X (mg/kg) × Y (kg)

4 Dose to be added into infusion bag:

Dose (mL) = XY mg/50 (mg/mL) where 50 mg/mL is durvalumab nominal concentration. The corresponding volume of durvalumab should be rounded to the nearest tenth mL (0.1 mL). Dose adjustments for each cycle are only needed for greater than 10% change in weight.

5 The number of vials required for dose preparation is the next greatest whole number of vials from the following formula:
Number of vials = Dose (mL) / 10.0 (mL/vial)

Example:

1 Cohort dose: 20 mg/kg
   (a) Patient weight: 30 kg
   (b) Dose for patient: 600 mg = 20 (mg/kg) × 30 (kg)

(c) Dose to be added into infusion bag:
Dose (mL) = 600 mg / 50 (mg/mL) = 12.0 mL

(d) The number of vials required for dose preparation:
Number of vials = 12.0 (mL) / 10.0 (mL/vial) = 2 vials

6.2.2 Study drug administration

Following a 7-day lead-in period (Cycle 0, AZD6738 monotherapy), each treatment cycle will span 28 days, as shown in Table 3.

Administration of AZD6738

When AZD6738 is administered, patients must fast (water to drink only) for at least 2 hours prior to taking a dose, to at least 1 hour post-dose for all doses.

AZD6738 will be administered for 7 days in Cycle 0 Days 1 to 7. AZD6738 will be administered orally 160 mg or 240 mg twice daily, approximately 12 hours apart, starting on Day 22 until Day 28 of each treatment cycle, starting with Cycle 1. Patients are allowed to take the scheduled dose up to 2 hours after the scheduled dose time. If greater than 2 hours, the missed dose should not be taken and patient should continue with next dose at allotted time. If a patient wishes to bring forward the time of their scheduled dose, the dose can be taken up to a maximum of 2 hours prior to the scheduled time, ie, ±2-hour window.

Administration of durvalumab

Following preparation of durvalumab (see Section 6.2.1), the entire contents of the IV bag should be administered as an IV infusion over approximately 60 minutes (±15 minutes).

Table 3 Treatment schedule, AZD6738 in combination with durvalumab

	Cycle 0	Cycle 1 (and beyond)		
	7-day lead-in	D1	D2 to D21	D22 to D28
AZD6738 (oral, bd)	X[a]			X
Durvalumab (IV)		X		

[a] AZD6738 monotherapy administered bd on each day of the 7-day lead-in.
bd twice daily; D day; IV intravenous.

Patients should continue to receive study treatment (ie, durvalumab in combination with AZD6738) until objective radiological disease progression as per Response Evaluation Criteria in Solid Tumours (RECIST 1.1), as long as, in the investigator's opinion, they are benefiting from treatment and they do not meet any other discontinuation criteria. Disease progression should be confirmed by a subsequent scan (no earlier than 4 weeks later) in the absence of clinically significant deterioration as assessed by the investigator. All patients who have objective progression of disease will enter follow-up.

6.2.3 Storage

All study drugs should be kept in a secure place under appropriate storage conditions.

The AZD6738 product label on the bottle specifies the appropriate storage.

Durvalumab is to be stored at the study centre in a secured facility with limited access and controlled temperature (2ºC to 8ºC). The study drug storage temperature should be monitored on a daily basis and documented in the temperature monitoring log according to the study drug handling instructions.

The study drug must be kept in the original outer container and under conditions specified on the labels.

In the following cases, the centre staff should not use affected study drug and should immediately contact AstraZeneca representative for further guidance:

- Temperature excursion upon receipt or during storage at the study
- Damaged kit upon receipt
- Damaged vial/bottle

Damaged study drug should be documented according to the instructions provided by AstraZeneca representative. Storage conditions stated in the Investigator's Brochure, or the study drug Handling Instructions document, may be superseded by the label storage.

6.2.4 Accountability

The study drugs provided for this study should only be used as directed in the study protocol.

The study site staff will account for all study drugs received at the centre, for unused study drugs, and for appropriate destruction (according to local procedures). Certificates of delivery, destruction, and/or return should be signed.

The administration of all medications (including study drug) and details of treatment with study drug should be recorded in the appropriate sections of the electronic Case Report Form (eCRF).

6.3 Measures to minimise bias: randomisation and blinding

This is an open-label study.

All patients will be centrally allocated to randomised cohorts using an IRT system. The randomisation will follow a 2:1 ratio to Cohort C.10.160 or Cohort C.10.240. The vendor will set up the randomisation process based on specifications that will be detailed in the study IRT documents. After pre-screening and eligibility criteria are verified, patients will be stratified

on their resistance type, before being randomly allocated to a cohort. This stratification will prevent imbalance between the 2 cohorts for that resistance factor.

Recruitment will not be paused during the interim analyses.

If a patient withdraws from participation in the study, then his/her enrolment code cannot be reused. Withdrawn patients will not be replaced.

There will be no blinding.

6.4 Treatment compliance

The administration of all study drugs should be recorded in the appropriate sections of the eCRF. Durvalumab will be administered on site. Treatment compliance will be assured by reconciliation of site drug accountability logs. Patients will record their oral AZD6738 dosing on a diary which should be returned to the site at the next available visit. Sites should additionally record AZD6738 doses taken at site visits.

Patients will self-administer AZD6738. Patients should be given clear instructions on how and when to take their study treatment. Study site staff will make tablet counts at regular intervals during treatment. Compliance will be assessed by the tablet count and the information will be recorded in the appropriate section of the eCRF. After the tablet count has been performed, the remaining tablets will not be returned to the patient but will be retained by the investigative site until reconciliation is completed by the study monitor. All patients must return their bottle(s) of AZD6738 at the appropriate scheduled visit, when a new bottle will be dispensed. Patients will be instructed to notify study site personnel of missed doses. Dates of missed or held doses will be recorded by the patient on their patient diary and by the site staff on the eCRF.

Patients must return all containers and any remaining tablets at their next scheduled treatment cycle and at the end of the study.

Any change from the dosing schedule, dose interruptions, dose reductions, dose discontinuations should be recorded in the eCRF. Note: Dose reductions are not allowed for durvalumab (see Section 6.6).

The Study Drug Storage Manager is responsible for managing the study drug from receipt by the study site until the destruction or return of all unused study drug. The investigator(s) is/are responsible for ensuring that the patient has returned all unused study drug.

Use of study treatment in doses in excess of that specified in the protocol is considered to be an overdose. Refer to Section 8.4.3 for procedures in case of overdose.

6.5 Concomitant therapy

Any medication or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the patient is receiving at the time of enrolment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Prohibited concomitant medications are described in Table 4. Please refer to Section 8.4.5 for guidance on management of study drug-related toxicities.

The use of concomitant medications must be recorded in the eCRF.

Table 4 Prohibited medications

Prohibited medication/class of drug:	Module 10 (HUDSON)
Unless stated otherwise, these medications are prohibited from the time that patients enter the main screening period until the last dose of study treatment. The pre-screen may be done whilst on prior therapy.	
Any investigational anticancer therapy other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment
Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment. (Note: concurrent use of hormones for non-cancer-related conditions [eg, insulin for diabetes and hormone replacement therapy] is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable [eg, by local surgery or radiotherapy]). Patients may receive treatment with bisphosphonates or RANKL inhibitors for the treatment of bone metastases
Immunosuppressive medications, including, but not limited to: systemic corticosteroids at doses exceeding 10 mg/day of prednisone or its equivalent, methotrexate, azathioprine, and tumour necrosis factor-α blockers	Should not be given concomitantly, or used for premedication prior to the infusions. The following are allowed exceptions: • Use of immunosuppressive medications for the management of study drug-related AEs • Short-term premedication for patients receiving combinations where the prescribing information for the agent requires the use of steroids for documented hypersensitivity reactions • Use in patients with contrast allergies • In addition, use of inhaled, topical, and intranasal corticosteroids is permitted. A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of non-immunotherapy related events experienced by the patient (eg, chronic obstructive pulmonary disease, radiation, nausea, etc).
Live attenuated vaccines	Prohibited from the time that patients enter the main screening period until 180 days after the last dose of study treatment.

Table 4 Prohibited medications

Prohibited medication/class of drug:	
Epidermal growth factor receptor (EGFR) Tyrosine kinase inhibitors (TKIs)	Should not be given concomitantly. Should be used with caution in the 90 days post last dose of durvalumab. Increased incidences of pneumonitis (with third generation EGFR TKIs) and increased incidence of transaminase increases (with 1st generation EGFR TKIs) have been reported when durvalumab has been given concomitantly.
Herbal and natural remedies which may have immune-modulating effects	Should not be given concomitantly unless agreed by the sponsor

AE adverse event

The use of herbal preparations/medications should be discouraged throughout the study. These herbal medications include, but are not limited to: St. John's Wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone, yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 7 days prior to first dose of study drug (3 weeks for St John's Wort). Use of these products, as well as use of all vitamins, nutritional supplements and all prescribed concomitant medications, must be recorded in the eCRF.

Other concomitant treatment

Medication other than that described above, which is considered necessary for the patient's safety and wellbeing, may be given at the discretion of the investigator and recorded in the appropriate sections of the eCRF.

6.5.1 Rescue and supportive medication

The study site will supply rescue medication, and this will be procured locally. The sponsor will supply only if required by local regulations.

The use of rescue medications is allowable at any time during the study. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

Supportive medication, described in Table 5, may be given at the discretion of the investigator and recorded in the appropriate sections of the eCRF.

Table 5 Supportive medication

Supportive medication/class of drug:	Usage:
Concomitant medications or treatments (eg, acetaminophen or diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care, except for those medications identified as "prohibited," as listed above	To be administered as prescribed by the investigator
Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy to non-target lesions, etc])	Should be used, when necessary, for all patients AZD6738 treatment should be discontinued for a minimum of 3 days before a patient undergoes palliative radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.
Inactivated viruses, such as those in the influenza vaccine or authorised and approved COVID-19 vaccines.	Permitted. Administration of COVID-19 vaccines should be avoided for 72 hours prior to administration of the first dose of study treatment.

COVID-19 Coronavirus Disease 2019.

6.5.2 Effect of AZD6738 on other drugs

Avoid concomitant medications, herbal supplements and/or ingestion of foods that significantly modulate CYP[CCI] or [CCI] activity (see guidelines below). Note: These include common azole antifungals, macrolide antibiotics, etc (please refer to Section 11 for details on AZD6738 drug-drug interactions). In the absence of discontinuation criteria, if the investigator feels that concomitant administration of medications, herbal supplements or foods that significantly modulate CYP[CCI] activity is necessary based upon medical judgement, such products may be administered with caution following discussion between the investigator and the study physician.

Concomitant medication may be given as medically indicated with the following exceptions:

- The principal enzyme for metabolising AZD6738 is CYP[CCI] Patients should avoid concomitant drugs, herbal supplements, and/or ingestion of foods known to modulate CYP[CCI] activity from the time they enter the screening period until 28 days after the last dose of study medication.
- AZD6738 is an inducer of CYP[CCI] CYP[CCI] and CYP[CCI] and showed weak inhibition of CYP[CCI] CYP[CCI] and CYP[CCI] Caution should be applied with co-administration of drugs that are either completely metabolised by CYP[CCI] and/or CYP[CCI] or CYP[CCI] or CYP[CCI] or that are substrates of CYP[CCI] and/or CYP[CCI] CYP[CCI] and CYP[CCI] and also have a narrow therapeutic index. Investigators should be aware that the exposure of other drugs metabolised by CYP[CCI] CYP[CCI] and/or CYP[CCI] may be increased and exposure of other drugs metabolised by CYP[CCI] and/or CYP[CCI] may be reduced.

- Strong CYP3CC inducers. For patients taking any of these drugs the required washout periods prior to starting AZD6738 is 2 weeks, except for St. John's Wort, which is 3 weeks.
- Prior to study medication, use of potent inducers or inhibitors of CYPCC are not permitted. For subjects taking any of these drugs, the required wash-out periods before starting AZD6738 is 5 half-lives; except for St. John's wort, which is 3 weeks.
- On study medication, if there is no suitable alternative concomitant medication other than a potent inhibitor of CYPCCI the investigator must interrupt AZD6738 for the duration of the potent CYPCC inhibitor and wait for the required wash-out period (5 half-lives) before dosing AZD6738 again. If potent CYPCC inducers are considered necessary for the patient's safety and welfare, this may diminish the clinical efficacy of AZD6738 and the patient should be monitored carefully for any change in the efficacy of study treatment.
- AZD6738 is also a P-gp substrate. Co-administration of CCI inhibitors or inducers may affect exposure to AZD6738 and therefore should not be co-administered with AZD6738 (please refer to Section 11 for details on AZD6738 drug-drug interactions). If the use of any inhibitors or inducers of P-gp are considered necessary for the patient's safety and welfare, the investigator must interrupt AZD6738 for the duration of the CCI inhibitor or inducer and wait for the required wash-out period of the CCI modulator (5 half-lives) before dosing with AZD6738.
- AZD6738 is a substrate of CCI Co-administration of CCI inhibitors or inducers may affect exposure to AZD6738 (please refer to Section 11 for details on AZD6738 drug-drug interactions); therefore, it is recommended that the investigators must interrupt AZD6738 for the duration of the BCRP inhibitor or inducer and wait for the required wash-out period of the CCI modulator (5 half-lives) before dosing AZD6738 again.
- AZD6738 is an inhibitor of CCI Co-administration of substrates of CCI may affect exposure to AZD6738; therefore, it is recommended that caution should be applied when such drugs are to be administered with AZD6738.
- The use of any natural/herbal products or other 'folk remedies' (and medications and foods that significantly modulate CYPCC) should be discouraged. If deemed necessary, such products may be administered with caution and the reason for use documented in the eCRF.
- Anticoagulation therapy: patients on warfarin may participate in this study but it is recommended that their INR is monitored more frequently.

6.6 Dose modification and discontinuation

For patients who weigh ≥30 kg, the dose of durvalumab cannot be modified. If a patient's body weight falls below 30 kg during the study, (s)he will be withdrawn from the study treatment unless (s)he derives some clinical benefit according to the treating physician. In this case, and following agreement between the treating physician and the sponsor, the patient may continue treatment at a body-weight adapted dose of 20 mg/kg actual body weight.

Durvalumab dosing can be interrupted in the event of treatment-related toxicity. All toxicities will be graded according to Common Toxicity Criteria for Adverse Events (CTCAE) version 4.03. Dose reductions are not permitted. In case of doubt, the investigator should consult with the study physician. Please refer to the toxicity management guidelines for durvalumab.

Dose adjustments for AZD6738 will be based on the organ system exhibiting the greatest degree of toxicity. Dose reductions or interruptions, and initiation of supportive care, are allowed as deemed appropriate by the treating physician. If Day 1 treatment with durvalumab is delayed, then AZD6738 will not resume until 22 days after the durvalumab dose is given. If durvalumab is delayed due to AZD6738-induced toxicity, please contact the sponsor for agreement on continuation of study therapy. Where a toxicity related event arises before AZD6738 is started within a cycle, AZD6738 must be started within up to 50 days from the prior administration of durvalumab. If the onset of AZD6738 is delayed, the onset of the subsequent durvalumab administration will need to be delayed accordingly. Where AZD6738 has been started within a given cycle, is interrupted and resumed within the planned 7-day dosing period, the patient must complete only the AZD6738 doses remaining until the last day of the planned 7-day period. There will be no opportunity to recover for any missed AZD6738 doses. If AZD6738 cannot be resumed within the planned 7-day period, then the patient will proceed to the next cycle, as planned. Any patient requiring a toxicity related dose delay of more than 50 days from the last day of dosing must be discontinued from the study treatment unless there is approval from the Study Physician for the patient to continue. A patient may continue on monotherapy if the other treatment is permanently stopped for drug-specific toxicity (not where the toxic effect is common to both drugs) (core protocol Section 7.1.1).

Study treatment should be stopped at least 3 days prior to planned surgery or radiotherapy. After surgery study treatment can be restarted when the wound has healed. No stoppage of study treatment is required for any biopsy procedure.

Table 6 AZD6738 dose modifications for toxicity management (7-day schedule)

Dose level	AZD6738 (160 mg starting dose)	AZD6738 (240 mg starting dose)
Initial dose	160 mg bd Days 22-28	240 mg bd Days 22-28
1st dose reduction	160 mg od Days 22-28	160 mg bd Days 22-28
2nd dose reduction	Stop treatment	160 mgod Days 22-28
3rd dose reduction	-	Stop treatment

bd twice daily;od once daily.

Management of study drug-related toxicities is described in detail in Section 8.4.5.

6.7 Treatment after the end of the study

Patients are permitted to either receive standard of care therapy, or to continue to receive study treatment following the end of the study if, in the opinion of the investigator, they are continuing to receive benefit from treatment. After discontinuation of study treatment, the investigator will be at liberty to define further most appropriate anti-cancer treatment. Subsequent anti-cancer treatment is expected to be initiated following the cancer recurrence or development of a new cancer. Information on subsequent anti-cancer therapies should be recorded on the clinical database.

7. DISCONTINUATION OF TREATMENT AND PATIENT WITHDRAWAL

Please refer to Section 7 in the core protocol. Stopping criteria for AZD6738 are in Section 8.4.5.2 of this module.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in the SoA (Table 1).

8.1 Efficacy assessments

Please refer to the core protocol.

8.2 Safety assessments

8.2.1 Clinical safety laboratory assessments

As part of the white blood cell count safety assessment, eosinophil and monocyte counts will be recorded.

Please refer to core protocol.

8.2.1.1 Coagulation

Please refer to core protocol.

8.2.1.2 Other safety assessments

Please refer to core protocol.

8.2.1.3 Pneumonitis (interstitial lung disease) investigation

The following assessments, and additional assessments if required, will be performed to enhance the investigation and diagnosis of potential cases of pneumonitis. The results of the assessment will be collected.

- Physical examination; Signs and symptoms (cough, shortness of breath and pyrexia, etc) including auscultation for lung field will be assessed.
- SpO_2; Saturation of peripheral oxygen (SpO_2)
- Other items; When pneumonitis (interstitial lung disease [ILD]) is suspected during study treatment, the following markers should be measured where possible:
  - ILD markers (KL-6, SP-D) and β-D-glucan
  - Tumour markers: Particular tumour markers which are related to disease progression.

8.2.2 Physical examinations

Please refer to core protocol.

8.2.3 Vital signs

Please refer to section 8.2.3 in the core protocol. However, if clinically indicated, eg, in the event of clinically relevant symptoms such as pre-syncope or dizziness, blood pressure will be

measured in the supine and standing positions after at least 10 minutes' rest. Assessments will be performed at the visits as shown in the SoA (Table 1).

8.2.4 Electrocardiograms

Please refer to core protocol.

8.2.5 Performance status

Please refer to core protocol.

8.3 Collection of adverse events

Please refer to the core protocol.

8.4 Safety reporting and medical management

8.4.1 Reporting of serious adverse events

Please refer to the core protocol.

Any myeloid malignancies (ie., MDS and/or AML) should be reported whenever this has been observed in the follow-up of the patients.

8.4.2 Pregnancy

Please refer to the core protocol.

8.4.3 Overdose

Please refer to the core protocol.

8.4.4 Medication error

Please refer to the core protocol.

8.4.5 Management of study drug-related toxicities

8.4.5.1 Management of durvalumab-related toxicities

Please refer to the toxicity management guidelines for durvalumab.

8.4.5.2 Management of AZD6738-related toxicities

If a patient experiences a clinically significant and/or unacceptable toxicity, dosing will be interrupted and supportive therapy administered as required.

If the toxicity resolves or reverts to CTCAE Grade ≤1 or 2 (depending on the toxicity), treatment with AZD6738 may be restarted using the rules in Table 7 for dose modifications. Patients who are at the lowest possible dose, or who had their dose previously reduced to the lowest possible dose and who have demonstrated an acceptable response to the dose

interruption may be permitted to restart at the lowest dose level at the discretion of the investigator.

If the toxicity does not resolve to CTCAE Grade ≤1 or 2 or the patient is not showing clinical benefit, then the patient should be discontinued from treatment and observed until resolution of the toxicity.

Any patient requiring a toxicity related dose delay of more than 28 days from the planned onset of AZD6738 (ie, 50 days from the last administration of durvalumab), must be discontinued from the study treatment, unless there is approval from the study physician for the patient to continue.

If a patient develops severe haematologic toxicity or blood transfusion dependence, treatment with AZD6738 should be interrupted and appropriate haematologic testing should be initiated. If the blood parameters remain clinically abnormal after 4 weeks of AZD6738 dose interruption, bone marrow analysis and/or blood cytogenetic analysis are recommended. If myeloid malignancies are confirmed whilst on treatment with AZD6738, it is recommended that AZD6738 should be discontinued and the patient be treated appropriately. AEs of myeloid malignancies should be monitored by conventional AE collection and reporting, additionally any cases should be reported after the 30-day follow-up period irrespective of Investigator causality.

The dose of AZD6738 must not be adjusted under any other circumstances than those described in this section unless prior agreement is given by the sponsor.

All dose modifications and interruptions (including any missed doses) and the reasons for the modifications/interruptions are to be recorded in the eCRF.

Table 7 Dose interruption and stopping criteria (7-day schedule)

Event	Action
Grade 1-2 toxicities (except Grade 2 neutropenia and thrombocytopenia)	AZD6738 dosing may continue with supportive treatment (as required) or investigator decision whether to interrupt AZD6738 (max 28 days). Following interruption, AZD6738 may be resumed at the same dose level.
Grade 2 neutropenia or Grade 3 anaemia	Blood counts may recover during the "off drug period" on the intermittent schedule. AZD6738 dosing may continue with supportive treatment (as required e.g. transfusion) or investigator decision whether to interrupt AZD6738 (max 28 days). Following interruption, AZD6738 may be resumed at the same dose level or dose reduced by 1 level[a].

Table 7 Dose interruption and stopping criteria (7-day schedule)

Event	Action
Grade 2-3 thrombocytopenia	**First occurrence** Interrupt AZD6738 (max 28 days) until platelets improve to ≥75,000/mm^3. Following interruption, AZD6738 may be resumed at the same dose level, as blood counts may recover during the "off period" on the intermittent schedule. If blood counts do not recover by the start of the next dosing period, AZD6738 should be restarted with a dose reduction by 1 level[a]. **Subsequent occurrences** Interrupt AZD6738 (max 28 days) until platelets improve to ≥75,000/mm^3. Following interruption, AZD6738 should be restarted with a dose reduction by 1 level[a].
Grade 4 thrombocytopenia	Interrupt AZD6738 (max 28 days) and give appropriate supportive treatment until platelets improve to ≥75,000/mm^3. Following interruption, AZD6738 should be restarted with a dose reduction by 1 level[a].
Grade 3-4 toxicity (including Grade 3-4 neutropenia or Grade 4 anaemia) *Excludes* Grade 3 anaemia or Grade 3-4 thrombocytopenia (see above)	**First occurrence** Interrupt AZD6738 (max 28 days) and give appropriate supportive treatment. When toxicity has resolved to grade 1, AZD6738 should be restarted with a dose reduction by 1 level[a]. **Subsequent occurrences** Investigator discretion on whether to interrupt AZD6738 (max 28 days) or to stop treatment. Following interruption, AZD6738 should be restarted with a dose reduction of 1 or 2 levels.
Vomiting	If vomiting occurs shortly after AZD6738 is swallowed, the dose should only be replaced if all of the intact tablets can be counted. Resume with the following scheduled dose.
Missed dose	Allowed to take the scheduled dose up to 2 hours after the scheduled dose time. If greater than 2 hours, the missed dose should not be taken and the patient should continue with next dose at the allotted time.

[a] This table is for guidance. Therefore, for example, it may be deemed appropriate by the investigator to reduce the dose by more than 1 dose level depending on the individual patient circumstances.

Individual stopping criteria:

Hepatic

- ALT or AST or ALP* > 5 × ULN
- ALT or AST or ALP* > 3 × ULN with the appearance of symptoms associated with a clinical diagnosis of hepatitis including right upper quadrant pain or tenderness, fever, rash or eosinophilia (> 5%)
- [ALT or AST > 3 × ULN] and [total bilirubin > 2 × ULN or INR+ > 1.5 or other evidence of impairment to the synthesis function of the liver]

* In the presence of bone metastasis, assess bone specific isoform of raised ALP in the presence of a raised gamma-GT (to ensure the ALP change is specific to the liver).

+ Unless patient is receiving warfarin.

Please refer to Appendix E "Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law".

Cardiovascular

Clinically significant hypotension defined as an asymptomatic decrease of more than 20 mmHg in systolic blood pressure to below 70 mmHg persisting for at least 10 minutes.

Symptomatic orthostatic fall in systolic blood pressure of more than 20 mmHg compared to resting supine systolic blood pressure.

Haematologic

Patients with suspected or with indications of MDS and/or AML must have the dose of AZD6738 stopped under all circumstances, and evidence of AML/MDS should be ruled out. Further treatment can only be accepted after discussion and agreement with the sponsor.

8.5 Pharmacokinetics

Refer to the core protocol.

8.6 Pharmacodynamics

Pharmacodynamic parameters will be evaluated in this study (see Section 8.6 of the core protocol).

8.7 Genetics

Refer to the core protocol.

8.8 Biomarkers

Refer to the core protocol.

8.9 Medical Resource Utilisation and Health Economics

Medical Resource Utilisation and Health Economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

Refer to the core protocol.

10. REFERENCES

Antonia et al 2019
Antonia SJ, Balmanoukian A, Brahmer J, Ou S-HI, Hellmann MD, Kim S-W, et al. Clinical activity, tolerability, and long-term follow-up of durvalumab in patients with advanced NSCLC. J Thorac Oncol. 2019;14(10)1794-806.

Cimprich and Cortez 2008
Cimprich KA, Cortez D. ATR: an essential regulator of genome integrity. Nat Rev Mol Cell Biol. 2008;9:616-27.

Forment and O'Connor 2018
Forment JV, O'Connor MJ. Targeting the replication stress response in cancer. Pharmacol Ther. 2018;188:155-67.

Galluzzi et al 2012
Galluzzi L, Senovilla L, Zitvogel L, Kroemer G. The secret ally: immunostimulation by anticancer drugs. Nat Rev Drug Discov. 2012;11(3):215-33

Garassino et al 2017
Garassino M, Vansteenkiste J, Joo-Hang Kim, Hervé Léna, MazièresJ, Powderly J, Dennis P, Huang Y, Wadsworth C, Rizvi N. PL04a.03: Durvalumab in ≥3rd-Line Locally Advanced or Metastatic, EGFR/ALK Wild-Type NSCLC: Results from the Phase 2 ATLANTIC Study. J Thor Onc. 2017;12:S10-S11.

Kim et al 2021
Kim ST, Smith SA, Mortimer P, Loembé A-B, Cho H, Kim K-M, et al. Phase I study of ceralasertib (AZD6738), a novel DNA damage repair agent, in combination with weekly paclitaxel in refractory cancer. Clin Cancer Res. 2021;27(17):4700-9.

Lee et al 2021
Lee J, Kim ST, Kim K, Lee H, Kozarewa I, Mortimer PGS et al. Tumor genomic profiling guides patients with metastatic gastric cancer to targeted treatment: The VIKTORY umbrella trial. Cancer Discov. 2019 Oct;9(10):1388-405.

Mahdi et al 2021
Mahdi H, Hafez N, Doroshow D, Sohal D, Keedy V, Do KT, et al. Ceralasertib-mediated ATR inhibition combined with olaparib in advanced cancers harboring DNA damage response and repair alterations (olaparib combinations). JCO Precis Oncol. 2021;5:PO.20.00439.

Mellman et al 2011
Mellman I, Coukos G, Dranoff G. Cancer immunotherapy comes of age. Nature. 2011;480:480-9.

Min et al 2017
Min A, Im S-A, Jang H, Kim S, Lee M, Kim DK et al. AZD6738, a novel oral inhibitor of ATR, induces synthetic lethality with ATM deficiency in gastric cancer cells. Mol Cancer Ther. 2017;16(4);566–77.

Nguyen et al 2018
Nguyen HD, Leong WY, Li W, Reddy PNG, Sullivan JD, Walter MJ, et al. Spliceosome mutations induce R loop-associated sensitivity to ATR inhibition in myelodysplastic syndromes. Cancer Res. 2018;78(18):5363-74.

Narwal et al 2013
Narwal R, Roskos LK, Robbie GJ. Population Pharmacokinetics of Sifalimumab, an Investigational Anti-Interferonalpha Monoclonal Antibody, in Systemic Lupus Erythematosus. Clin Pharmacokinet. 2013;52:1017–27.

Ng et al 2006
Ng CM, Lum BL, Gimenez V, Kelsey S, Allison D. Rationale for fixed dosing of pertuzumab in cancer patients based on population pharmacokinetic analysis. Pharm Res. 2006;23(6):1275–84.

O'Connor 2015
O'Connor MJ. Targeting the DNA Damage Response in Cancer. Mol Cell. 2015;60:547-60.

Parkes et al 2017
Parkes EE, Walker SM, Taggart LE, McCabe N, Knight LA, Wilkinson R et al. Activation of STING-Dependent Innate Immune Signaling By S-Phase-Specific DNA Damage in Breast Cancer. J Natl Cancer Inst. 2017;109(1).

Rizvi et al 2020
Rizvi NA, Cho BC, Reinmuth N, Lee KH, Luft A, Ahn M-J, et al. Durvalumab with or without tremelimumab vs standard chemotherapy in first-line treatment of metastatic non-small cell lung cancer: The MYSTIC Phase 3 randomized clinical trial. JAMA Oncol. 2020;6(5):661-674.

Shah et al 2021
Shah PD, Wethington SL, Pagan C, Latif N, Tanyi J, Martin LP, et al. Combination ATR and PARP Inhibitor (CAPRI): A phase 2 study of ceralasertib plus olaparib in patients with recurrent, platinum-resistant epithelial ovarian cancer. Gynecol Oncol. 2021;163(2):246-253.

Stewart et al 2015
Stewart R, Morrow M, Hammond SA, Mulgrew K, Marcus D, Poon E et al. Identification and characterization of MEDI4736, an antagonistic anti-PD-L1 monoclonal antibody. Cancer Immunol Res. 2015;3(9):1052-62.

Toledo et al 2011
Toledo LI, Murga M, Zur R, Soria R, Rodriguez A, Martinez S et al. A cell-based screen identifies ATR inhibitors with synthetic lethal properties for cancer-associated mutations. Nat Struct Mol Biol. 2011;18:721-7.

Wang et al 2009
Wang DD, Zhang S, Zhao H, Men AY, Parivar K. Fixed dosing versus body size based dosing of monoclonal antibodies in adult clinical trials. J Clin Pharmacol. 2009;49(9):1012-24.

Weber and Ryan 2015
Weber AM, Ryan AJ. ATM and ATR as therapeutic targets in cancer. Pharmacol Ther. 2015;149:124-38.

Williamson et al 2016
Williamson CT, Miller R, Pemberton HN, Jones SE, Campbell J, Konde A, et al. ATR inhibitors as a synthetic lethal therapy for tumours deficient in ARID1A. Nat Commun. 2016;7:13837.

Zhang et al 2012
Zhang S, Shi R, Li C, Parivar K, Wang DD. Fixed dosing versus body size-based dosing of therapeutic peptides and proteins in adults. J Clin Pharmacol. 2012;52(1):18–28.

11. AZD6738 DRUG-DRUG INTERACTIONS

Restrictions regarding drugs affecting CYP[CC] metabolism

There are currently no data confirming that there is a pharmacokinetic (PK) interaction between drugs that affect CYP[CC] metabolism and AZD6738; a potential interaction is considered on the basis of preclinical and in vitro data only. AZD6738 is predominantly eliminated via CYP[CC] metabolism, therefore CYP[CC] inhibitors or inducers may increase or decrease exposure to AZD6738, respectively. Potent inhibitors or inducers of CYP[CC] should not be combined with AZD6738. In vitro data also suggest that AZD6738 may be metabolised by CYP[CCI] to a lesser extent, therefore caution should be applied with co-administration of potent inhibitors or inducers of CYP[CCI]

Drugs known to be inhibitors and inducers of CYP[CC] or CYP[CCI] are listed in Table 8 and Table 9, respectively. These lists are not intended to be exhaustive, and similar restrictions will apply to other agents that are known to modulate CYP[CC] or CYP[CCI] activity. Please contact AstraZeneca with any queries on this issue. Please refer to full prescribing information for all drugs prior to co-administration with AZD6738.

Table 8 Drugs known to be inhibitors and inducers of CYPCC

Potent CYPC inhibitors	Potent CYPC inducers
boceprevir	apalutamide
ceritinib	avasimibe
clarithromycin	carbamazepine
cobicistat (GS-9350)	ceralasertib
conivaptan	enzalutamide
danoprevir / RIT	ivosidenib
elvitegravir / RIT	lumacaftor
grapefruit juice[a]	mitotane
idelalisib	phenobarbital
indinavir	phenytoin
indinavir /RIT	rifampin
itraconazole	rifapentine
ketoconazole	St John's Wort extract
LCL161	
lopinavir / RIT	
mibefradil	
mifepristone	
nefazodone	
nelfinavir	
posaconazole	
ribociclib	
ritonavir	
saquinavir	
saquinavir / RIT	
telaprevir	
telithromycin	
tipranavir/RIT	
troleandomycin	
VIEKIRA PAK2[b]	
voriconazole	

[a] Double-strength grapefruit juice. Patients should abstain from eating large amounts of grapefruit and Seville oranges (and other products containing these fruits eg, grapefruit juice or marmalade) during the study (eg, no more than a small glass of grapefruit juice (120 mL) or half a grapefruit or 1 to 2 teaspoons (15 g) of Seville orange marmalade daily.

[b] VIEKIRA PAK = 150/100 mg paritaprevir/ritonavir + 25 mg ombitasvir + 800 mg dasabuvir for 28 days.

List created using the University of Washington Drug-Drug Interaction Database July 2019.

RIT Ritonivir. Ritonavir has dual effects of simultaneous CYPC inhibition and induction, and the net pharmacokinetic outcome during chronic ritonavir therapy is inhibition of CYPC activity

Table 9 Drugs known to be inhibitors and inducers of CYP[redacted]

Potent CYP[redacted] inhibitors	**Potent CYP[redacted] inducers**
gemfibrozil clopidogrel	None identified

List created using the University of Washington Drug-Drug Interaction Database Jan 2020.

Drugs known to be inhibitors or inducers of [redacted] undertake appropriate monitoring if co-administration is necessary

AZD6738 is a substrate of [redacted]. Co-administration of [redacted] inhibitors/inducers or [redacted] inhibitors/inducers may affect exposure to AZD6738, therefore it is recommended that these are not co-administered with AZD6738.

Drugs known to be inhibitors or inducers of [redacted] are listed in Table 10 and Table 11, respectively. These lists are not intended to be exhaustive, and similar restrictions will apply to other agents that are known to modulate [redacted]. Please contact AstraZeneca with any queries on this issue. Please refer to full prescribing information for all drugs prior to co-administration with AZD6738.

Table 10 Drugs known to be inhibitors or inducers of CCI

Drugs Known to be Inhibitors of CCI	Drugs Known to be Inducers of CCI
alogliptin	apalutamide
amiodarone	avasimibe
asian ginseng (Panax ginseng)	carbamazepine
asunaprevir	danshen (Salvia miltiorrhiza)
AZD5672	efavirenz
azithromycin	genistein
canagliflozin	green tea
captopril	phenytoin
carvedilol	quercetin
clarithromycin	rifabutin
clopidogrel	rifampin
cobicstat	ritonavir
conivaptan	St. John's wort extract
cremophor EL	tivantinib
cremophor RH	
curcumin	
daclatasvir	
daclatasvir/asunaprevir/beclabuvir	
diltiazem	
diosmin	
dronedarone	
elagolix	
eliglustat	
erythromycin	
felodipine	
five-flavor berry (schisandra chinensis)	
flibanserin	
fluvoxamine	
fostamatinib	
ginkgo	
glecaprevir/pibrentasvir	
indinavir	
indinavir/ritonavir	
isavuconazole	
itraconazole	
ivacaftor	
ketoconazole	
lapatinib	
lopinavir/ritonavir	
mibefradil	

Table 10 Drugs known to be inhibitors or inducers of CCI

mifepristone	
milk thistle	
mirabegron	
nelfinavir	
neratinib	
nifedipine	
nitrendipine	
osimertinib	
paritaprevir/ritonavir/ombitasvir	
paroxetine	
piperine	
propafenone	
quercetin	
quinidine	
quinine	
ranolazine	
rifampin	
ritonavir	
rolapitant	
rucaparib	
saquinavir/ritonavir	
sarecycline	
simeprevir	
sofosbuvir/velpatasvir/voxilaprevir	
St. John's wort extract	
surfactant TPGS	
suvorexant	
talinolol	
telithromycin	
telaprevir	
telmisartan	
tezacaftor/ivacaftor	
ticagrelor	
tipranavir/ritonavir	
tolvaptan	
valbenazine	
valspodar (PSC 833)	
vandetanib	
velpatasvir	
vemurafenib	
verapamil	

Table 10 Drugs known to be inhibitors or inducers of CCI

voclosporin vorapaxar	

List created using the University of Washington Drug-Drug Interaction Database October 2019.

Table 11 Drugs known to be inhibitors or inducers of CCI

Drugs Known to be Inhibitors of CCI	Drugs Known to be inducers of CCI
afatinib aripiprazole curcumin cyclosporine elacridar erlotinib fluvastatin fumitremorgin gefitinib ivermectin lapatinib nilotinib novobiocin pantoprazole pitavastatin ponatinib quercetin quizartinib rabeprazole regorafenib rilpivirine sulfasalazine sunitinib tacrolimus teriflunomide trametinib trifluoperazine vismodegib eltrombopag atazanavir lopinavir ritonavir tipranavir omeprazole	Please check individual drugs on a case-by-case basis

Table 11 Drugs known to be inhibitors or inducers of CCI

estrone 17b-estradiol imatinib mesylate	

List created using http://dmd.aspetjournals.org/content/dmd/43/4/490.full.pdf
Note: Although CCI is involved in a number of clinically relevant DDIs, none of the listed inhibitors above is truly specific for this transporter

Drugs known to be substrates of CYP[CCI] and/or CYP[CCI] or CYP[CCI] or CYP[CCI] undertake appropriate monitoring if co-administration is necessary

AZD6738 is an inducer of CYP[CCI] CYP[CCI] and CYP[CCI] and showed weak inhibition of CYP[CCI] CYP[CCI] and CYP[CCI]. Therefore, caution should be applied with co-administration of drugs that are either completely metabolised by CYP[CCI] and/or CYP[CCI] or CYP[CCI] or CYP[CCI] or that are substrates of CYP[CCI] and/or CYP[CCI] CYP[CCI] and CYP[CCI] and also have a narrow therapeutic index (Table 12). Investigators should be aware that the exposure of other drugs metabolised by CYP[CCI] CYP[CCI] and/or CYP[CCI] may be increased, and exposure of other drugs metabolised by CYP[CCI] and/or CYP[CCI] may be reduced.

Table 12 Drugs known to be metabolised by CYP[CCI] and/or CYP[CCI] CYP[CCI] and CYP[CCI]

Metabolised by CYP[CCI]	Metabolised by CYP[CCI]	Metabolised by CYP[CCI]	Metabolised by CYP[CCI]
Abemaciclib (NTR)	agomelatine	daprodustat	benzbromarone
ABT-384	alosetron[a]	dasabuvir	celecoxib
Acalabrutinib (NTR)	caffeine	repaglinide[b]	ibuprofen
alfentanil	duloxetine		(R)-ibuprofen
alisporivir	melatonin		(S)-ibuprofen
almorexant	pirfenidone		glimepiride
alpha-dihydroergocryptine	ramelteon[a]		glipizide
aplaviroc	selegiline[a]		lornoxicam
aprepitant	tacrine		meloxicam
asunaprevir	tasimelteon[a]		piroxicam
atazanavir	tizanidine (NTR)		(S)-warfarin (NTR)
atorvastatin			tolbutamide
avanafil			
avapritinib			
AZD1305			
BIRL 355			
blonanserin			
bosutinib (NTR)			
brecanavir			
brotizolam			
budesonide			
buspirone			
BZF961			
capravirine			
casopitant			
cobimetinib (NTR)			
conivaptan (NTR)			
danoprevir			

Table 12 Drugs known to be metabolised by CYP[CCI] and/or CYP[CCI] CYP[CCI] and CYP[CCI]

darifenacin darunavir dasatinib (NTR) dronedarone ebastine eletriptan eliglustat (in subjects CYP[CCI] PMs) elvitegravir entrectinib (NTR) eplerenone everolimus felodipine ibrutinib indinavir isavuconazole itacitinib ivabradine ivacaftor L-771,688 Levomethadyl/Levacetymethadol (LAAM) (NTR) Lomitapide (NTR) lonafarnib lopinavir lovastatin lumefantrine lurasidone maraviroc midazolam midostaurin (NTR) morphothiadin naloxegol neratinib (NTR) nisoldipine paritaprevir4 perospirone pyrotinib quetiapine ridaforolimus			

Table 12 Drugs known to be metabolised by CYP[CCI] and/or CYP[CCI] CYP[CCI] and CYP[CCI]

saquinavir			
sildenafil			
simeprevir			
simvastatin			
sirolimus			
tacrolimus			
terfenadine			
ticagrelor			
tilidine3			
tipranavir			
tolvaptan (NTR)			
triazolam			
ubrogepant			
ulipristal			
vardenafil			
venetoclax (NTR)			
vicriviroc			
vilaprisan			
voclosporin			
zanubrutinib (NTR)			

[a] Complex Interaction -Substrates metabolized by multiple enzymes, including CYP[CCI]
[b] Repaglinide is also a substrate of [CCI] which might also be inhibited by gemfibrozil or its glucuronide.
List created using the University of Washington Drug-Drug Interaction Database August 2021. Note: This is not an exhaustive list.
(NTR) drug listed in the Narrow Therapeutic Index list by CYP isoform in DrugBank.

Drugs known to be substrates of [CCI] undertake appropriate monitoring if co-administration is necessary

AZD6738 is also an inhibitor of [CCI] Caution should be applied with co-administration of substrates of [CCI] as AZD6738 may increase their exposure.

Drugs known to be substrates of [CCI] are listed in Table 13 and Table 14, respectively. These lists are not intended to be exhaustive and appropriate medical judgment is required. Please contact AstraZeneca with any queries on this issue. Please refer to full prescribing information for all drugs prior to co-administration with AZD6738.

Table 13 Drugs known to be substrates of [redacted]

docetaxel
enalapril
olmesartan
phalloidin
repaglinide
statins[a]
temocaprilat
valsartan

[a] All statins

List created using https://www.solvobiotech.com/transporters/[redacted], latest access Nov 2019

Table 14 Drugs known to be substrates of [redacted]

anthracyclines
chlorothiazide
daunorubicin
doxorubicin
imatinib
irinotecan
methotrexate
mitoxantrone
nucleoside analogs
pantoprazole
prazosin
SN-38
topotecan
teriflunomide
rosuvastatin

List created using https://www.solvobiotech.com/transporters/[redacted] latest access Nov 2019

Clinical Study Protocol	
Drug Substance	Umbrella study
Study Code	D6185C00001 (HUDSON)
Version	14.0
Date	09 October 2024

Appendix S

Module 11: AZD6738 (ceralasertib) monotherapy

An Open-Label, Multi-Drug, Biomarker-Directed, Multi-Centre Phase II Umbrella Study in Patients with Non-Small Cell Lung Cancer, who Progressed on an Anti-PD-1/PD-L1 Containing Therapy (HUDSON)

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

Regulatory Agency Identification Numbers:

EudraCT number: 2017-002208-28

EU CT number: 2023-509004-15-00

IND number: 138050

VERSION HISTORY

Version 14.0, 09 October 2024

Key amendments and rationale for changes:

Section 2.2.1.3, AZD6738 monotherapy safety data: CCI [redacted] when AZD6738 is used as monotherapy and in combination with durvalumab.

Section 6.5.2, drug-drug interaction between AZD6738 and other drugs; Section 11, AZD6738 drug-drug interactions: Updated to describe AZD6738 as an inducer of CYPCCI CYPCCI and CYPCCI and a weak inhibitor of CYPCCI and CYPCCI

Section 8.4.1, reporting of serious adverse events: addition of text relating to the reporting of MDS and/or AML during follow-up.

Section 8.4.5, management of study drug-related toxicities:

- Guidance was added for patients who experience suspected MDS/AML.
- New sub-section was added to describe actions to be taken if a patient displays suspected indications of MDS and/or AML.

Table 8, drugs known to be inhibitors and inducers of CYPCC: Ceralasertib was added as a potent CYPCC inducer.

Minor text clarifications were also made.

Version 13.0, 14 December 2023

Key amendments and rationale for changes:

Front page: EU CT number has been added in line with the core CSP.

Table 1, schedule of activities:

- Footnote g) was split into two separate footnotes, g) and h), and clarified.
- Footnote i) was added to clarify the end of treatment visit timepoint when the patient is eligible for subsequent treatment with the combination of durvalumab + AZD6738.
- Footnote j) was updated to clarify that CCI sample at the end of treatment is not required for patients switching to combination treatment.

Section 6.1.1, study drugs: Text regarding 'Packaging and Labelling' updated to remove the information that labels will fulfil GMP Annex 13 requirements for labelling, as this Annex has been replaced.

Section 6.2.1, study drug administration:

- Updated to remove the prohibition on extending treatment beyond day 7, as this is not a necessary condition for AZD6738 administered as monotherapy.
- Updated to clarify that progression on AZD6738 monotherapy must be confirmed as per RECIST.

Section 6.7, treatment after the end of study: Updated to clarify the schedule for the transition to combination treatment.

Table 6, schedule of activities – combination of AZD6738 + durvalumab after the end of Module 11 monotherapy:

- Title was updated to clarify that it refers to the combination of AZD6738 + durvalumab.
- Cycle 0 column was added.
- Week numbers for Cycles 1 and 2 were corrected.
- Clinical chemistry and haematology assessments were added to Day 22 of Cycles 1 and 2.
- ADA sampling was removed as it is not applicable to patients in this treatment module who have transitioned to combination therapy.
- Subsequent cancer therapy and survival status assessments were removed as these are not applicable to patients in this treatment module who have transitioned to combination therapy.
- Footnote d) was added to clarify the circumstances under which Cycle 0 is applicable; footnotes e) and f) were added to clarify that safety assessments should not be repeated in circumstances where they have been performed as part of the end of monotherapy treatment visit; footnote g) was added to clarify the management of the additional laboratory assessments on Day 22 of Cycles 1 and 2; footnote h) was added to clarify the window for durvalumab administration.
- Other minor text clarifications were also made.

Section 9, statistical considerations: updated to add specific details regarding the safety analysis in Module 11.

Version 12.0, 01 March 2023

Key amendments and rationale for changes:

Table 1, schedule of activities:

- Removal of thyroid function parameters from the laboratory assessments. As the study treatment for this module does not include durvalumab, the evaluation of these parameters is not required.
- The visit in which flow cytometry samples are to be collected was updated in the footnote.

Table 1, schedule of activities; Section 6.2.1, study drug administration; Section 6.7, treatment after the end of the study: Updated to clarify the circumstances in which Investigators may offer subsequent study treatment with the combination of durvalumab + AZD6738 in patients who have progressed on initial AZD6738 monotherapy; introduction of a schedule of assessments for these patients.

Section 2.2.1.1, overview of AZD6738; Section 2.2.1.2 AZD6738 clinical programme; Section 2.2.1.3, AZD2736 monotherapy safety data: Updated in line with the AZD6738 IB Edition 11.

Section 2.2.1.4, Emerging data from Module 3 and Module 8 of HUDSON and rationale for assessing AZD6738 monotherapy in Module 11: Data updated up the cut-off dated of 26 October 2022.

Section 5.2, exclusion criteria (Module 11-specific): Changed to align the exclusion criteria with the current AZD6738 project specific safety requirements (SSPR)

- Exclusion criterion S-4: Addition of text in bold:
  Inadequate bone marrow reserve or organ function as demonstrated by any of the following laboratory values: absolute neutrophil count <1.5 x 10^9/L; platelet count <100 x 10^9/L; haemoglobin <90 g/L, **with no blood transfusion (packed red blood cells) in the past 28 days.**
- Exclusion criterion S-6: Changed creatinine clearance from <45 mL/min to <40 mL/min

Section 6.2, preparation/handling/storage/accountability: Added a reference to the Pharmacy Manual.

Section 6.6, dose modification and discontinuation: Updated to clarify the CTCAE version to be used for toxicities grading.

Section 6.6, dose modification and discontinuation; Section 8.4.5, management of study drug-related toxicities: Updated to clarify the length of time of a toxicity related dose delay to consider discontinuing patients from study. **Section 10, references:** The list of references was updated in line with the citations in the text.

Version 11.0, 16 August 2022
Initial creation of Module 11. Version number 11.0 used for consistency with the rest of the protocol.

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

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1. PROTOCOL SUMMARY

1.1 Schedule of Activities (SoA)

The Schedule of Activities (SoA) for the on-treatment period for Module 11 is shown in Table 1. For the SoA for the pre-screening and main screening visits, please refer to the core protocol.

Table 1 Schedule of Activities – Treatment intervention period (Module 11)

	C1 28 days Weeks 1-4		**C2** 28 days Weeks 5-8		**C3 - etc** All cycles 28 days		**Study drug disc.** (28 days after study drug disc.) [i]	**Safety follow-up** (90 days after study drug disc.)[a]	**Survival follow up**	**Notes**
Week	**1**	**2**	**5**	**6**	**9, 13, 17 etc (D1 of each cycle)**					
Day of cycle	**1**	**8**	**1**	**8**	**1**	**8[b]**				
Window (days)	**0[c]**	**+1**	**+1**	**+1**	**+1**	**+1**	**±7**	**±7**	**±7**	
Study procedures[d]										
Physical examination	X	X (if clinically indicated)	X	X (if clinically indicated)	X	X (if clinically indicated)	X			Section 8.2.2 (core protocol)
Vital signs[e]	X	X	X	X	X	X	X			Section 8.2.3 (core protocol)
ECG	X		X		X					Section 8.2.4 (core protocol)
Concomitant medications	X	X	X	X	X	X	X			Section 6.5
Laboratory assessments[d]										
Clinical chemistry	X[f]	X[f]	X[f]	X[f]	X	X	X			Section 8.2.1 (core protocol). If screening laboratory assessments are performed within 3 days prior to Day 1 they do not need to be repeated
Haematology	X[f]	X[f]	X[f]	X[f]	X	X	X			
APTT and INR	X	As clinically indicated								

	C1 28 days Weeks 1-4		C2 28 days Weeks 5-8		C3 - etc All cycles 28 days		Study drug disc. (28 days after study drug disc.) [i]	Safety follow-up (90 days after study drug disc.)[a]	Survival follow up	Notes
Week	**1**	**2**	**5**	**6**	**9, 13, 17 etc (D1 of each cycle)**					
Day of cycle	**1**	**8**	**1**	**8**	**1**	**8[b]**				
Window (days)	**0[c]**	**+1**	**+1**	**+1**	**+1**	**+1**	**±7**	**±7**	**±7**	
Urinalysis	X	As clinically indicated								Section 8.2.1 (core protocol)
Pregnancy test	X		X		X		X			Section 8.2.1.2 (core protocol)
AE/SAE	X	X	X	X	X	X	X	X		Section 8.3 (core protocol)
Study drug administration[d]										
AZD6738[g, h]	X Days 1-7		X Days 1-7		X Days 1-7					Section 6.1
Drug accountability	X	X	X	X	X	X	X			Section 6.2.3
Other administration										
Blood for [redacted] assessments[j]	X		X		X		X			Section 8.8 (core protocol)
Circulating soluble factors	X	X	X	X	X (Cycle 3 only)					Section 8.8 (core protocol)
Whole blood for gene expression (PAXgene RNA tubes)	X		X		X (Cycle 3 only)					Section 8.8 (core protocol)
Whole blood for flow cytometry (immunophenotyping)[k]	X	X	X	X	X (Cycle 3 only)					Section 8.8 (core protocol)

	C1 28 days Weeks 1-4		**C2** 28 days Weeks 5-8		**C3 - etc** All cycles 28 days		**Study drug disc.** (28 days after study drug disc.) [i]	**Safety follow-up** (90 days after study drug disc.)[a]	**Survival follow up**	**Notes**
Week	**1**	**2**	**5**	**6**	**9, 13, 17 etc (D1 of each cycle)**					
Day of cycle	**1**	**8**	**1**	**8**	**1**	**8[b]**				
Window (days)	**0[c]**	**+1**	**+1**	**+1**	**+1**	**+1**	**±7**	**±7**	**±7**	
TCR immuno-sequencing	X	X	X	X	X (Cycle 3 only)					Section 8.8 (core protocol)
Tumour evaluation (CT or MRI, RECIST 1.1)		Every 6 weeks ±1 week for the first 24 weeks relative to the start of therapy (Cycle 1 Day 1), then every 8 weeks ±1 week thereafter, until objective disease progression as defined by RECIST 1.1 and confirmed with a subsequent scan (in the absence of clinically significant deterioration)								Section 8.1 (core protocol)
Biopsy on treatment (mandatory)[l]			X							Section 8.8 (core protocol). This should align with the first RECIST assessment
Biopsy on disease progression (optional)							X			Section 8.8 (core protocol)
Subsequent cancer therapy								X	X	Section 8.1.3.1 (core protocol). To be done every 3 months
Survival status									X[m]	Section 8.1.3.1 (core protocol). To be done every 3 months

[a] If appropriate, the safety follow-up can be a telephone contact with the patient with the information recorded in the eCRF.

[b] Patients who develop an event ≥ Grade 3 of thrombocytopenia, anaemia and/or neutropenia later in their treatment will also need to have this additional assessment until there is no evidence of ≥ Grade 3 thrombocytopenia, anaemia and/or neutropenia for at least 2 cycles.

[c] Every effort should be made to minimise the time between allocation and starting treatment. Note, if main screening assessments have been performed within 3 days prior to C1D1, then assessments do not need to be performed on C1D1 pre-dose.

[d] Following the final data cut off for final analysis, for patients who do continue to receive treatment beyond the time of the final data cut-off, investigators will continue to report all SAEs, pregnancy, and overdose until 90 days after the last dose of study treatment, in accordance with Section 8.4.1 of the core CSP using paper forms. Additionally, in accordance with Section 4.4 of the core CSP, any SAE that is ongoing at the time of the final data cut-off must be followed up to resolution unless the event is considered by the investigator to be unlikely to resolve, or the patient is lost to follow-up.

[e] If clinically indicated, blood pressure to be measured in the supine and standing positions after at least 10 minutes' rest.

[f] Haematology and clinical chemistry assessments will take place on Day 1 and Day 8 (± 1-day window) of Cycles 1 and 2. If any toxicity is detected during these additional safety assessments, the patient will be managed as per the protocol, and as clinically indicated. In the event that a patient has an event of thrombocytopenia, anaemia and/or neutropenia that is ≥ Grade 3 during the first 2 cycles, this additional safety assessment will be included in subsequent cycles until there is no evidence of ≥ Grade 3 thrombocytopenia, anaemia and/or neutropenia for at least 2 cycles.

[g] Patients must receive AZD6738 for 7 days within a 28-day cycle. A cycle must not be < 28 days. AZD6738 must not be given on any other days of the cycle, and dosing days must stay relative to Day 1 of each cycle. In case of drug interruption within the planned Day 1 to 7 dosing window (for any reason), resumption of treatment can only take place within the planned dosing window and not beyond, even if this means the patient receives less than the specified 7 days AZD6738 dosing in the particular cycle.

[h] There will be an option for patients with progressive disease on AZD6738 monotherapy to have durvalumab added on their AZD6738 treatment, for as long as this is considered in the patient's best interest by the Investigator, and with approval of the sponsor. As the combination treatment durvalumab + AZD6738 is still a non-approved therapy, this will need to be considered as study medication and will require safety assessments accordingly (see Section 6.7). This will not be considered as a re-allocation to Module 10.

[i] When switching to combination treatment, if the patient can start the combination treatment immediately after the end of monotherapy, the end of treatment visit of AZD6738 monotherapy will be performed before the administration of durvalumab on C1D1 of the combination treatment (see Section 6.7). If the patient cannot start the combination treatment immediately after the monotherapy, the end of treatment visit of AZD6738 monotherapy will be performed 28 ±7 days after the last dose of AZD6738 and prior to initiating combination treatment.

[j] Whole blood for CCI will be taken every cycle for the first 3 cycles and then at every radiographic assessment visit (every 6 weeks [± 1 week] for the first 24 weeks relative to the start of therapy (C1D1), then every 8 weeks [± 1 week] in all patients (at pre-dose on AZD6738 dosing day), until disease progression (or study treatment discontinuation). A CCI sample at the end of treatment is not required for patients switching to combination treatment.

[k] Sample collection is for up to 20 patients only. If a flow cytometry sample is not collected at the C1D1 visit, there is no requirement to collect further samples for analysis at subsequent study visits.

[l] On-treatment biopsy is not required if a fresh tumour sample is not collected at pre-screening.

[m] Ad hoc collection of survival status may be requested for overall survival analyses.

AE = adverse event; APTT = activated partial thromboplastin time; C = cycle; CSP = clinical study protocol; CSR = clinical study report; CT = computed tomography; CCI; D = day; ECG electrocardiogram; eCRF = electronic Case Report Form; INR = international normalised ratio; MRI = magnetic resonance imaging; RECIST 1.1 = Response Evaluation Criteria in Solid Tumours 1.1; SAE = serious adverse event; TCR = T-cell receptor repertoire.

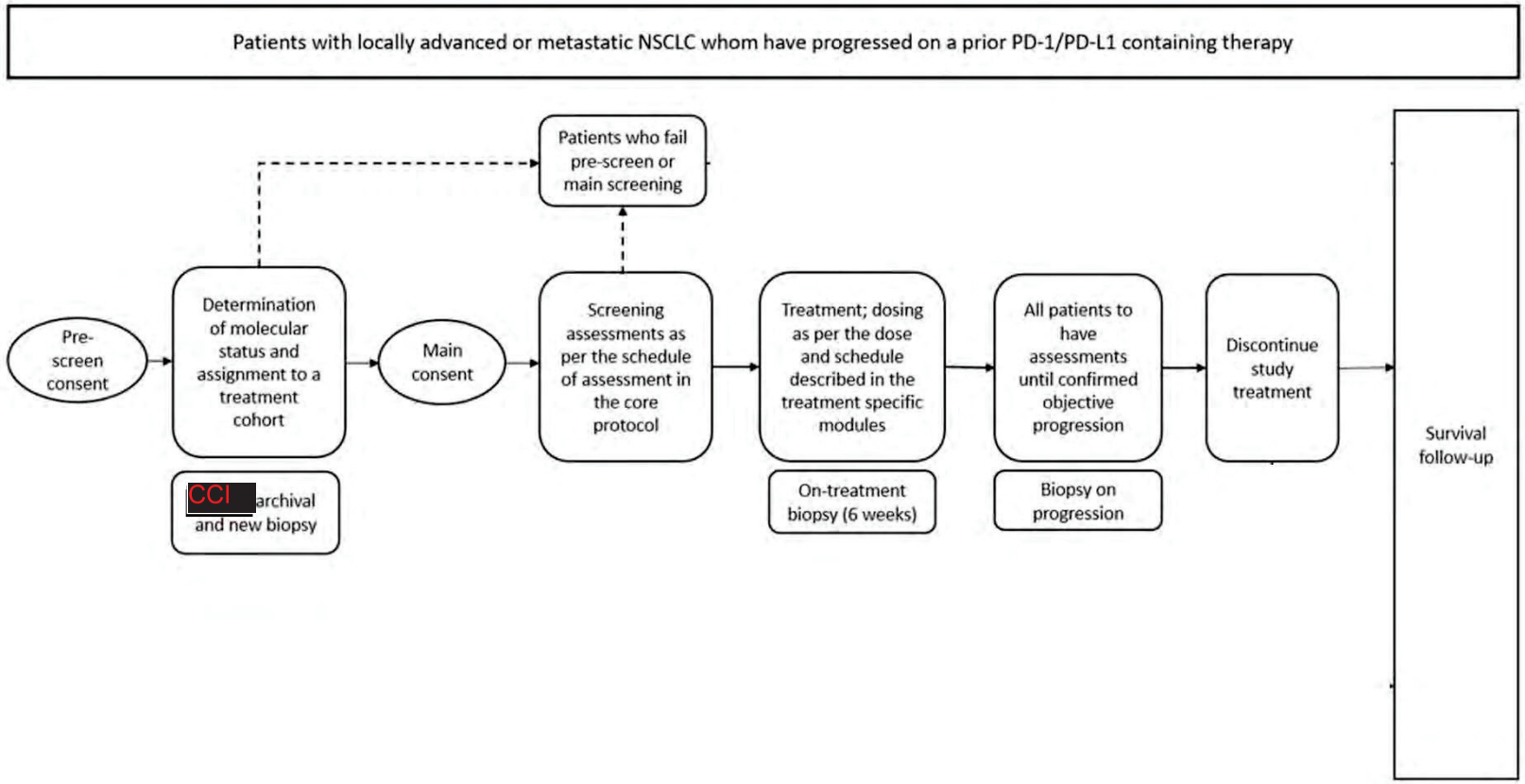
1.2 Synopsis

Please refer to Section 1.2 of the core protocol.

1.3 Schema

The general study design is summarised in Figure 1.

Figure 1 Study design



CCI NSCLC = non-small cell lung cancer; PD-1 = programmed cell death-1; PD-L1 = programmed cell death-ligand 1.

2. INTRODUCTION

Study D6185C00001 (HUDSON) is a Phase II, open-label, multi-centre umbrella study in patients who have received an anti-programmed cell death-1 (PD-1)/anti-programmed cell death-ligand 1 (PD-L1) containing therapy and a platinum-doublet regimen for locally advanced or metastatic non-small cell lung cancer (NSCLC) either separately or in combination. The patient must have had disease progression on a prior line of anti-PD-1/PD-L1 therapy. This module to the core study protocol describes Module 11, which will investigate the efficacy, safety, and tolerability of AZD6738 monotherapy at a dose of 240 mg twice daily (bd) for 7 consecutive days.

2.1 Study rationale

As described in Section 2.2 of the core protocol, immune checkpoint inhibitors targeting the PD-1/PD-L1 pathway have shown significant activity in the first- and second-line treatment settings in patients with NSCLC. However, it is becoming evident that there is a new and significant patient population emerging that does not respond to anti-PD-1/PD-L1 containing therapy (primary resistance) or progresses during anti-PD-1/PD-L1 containing therapy (acquired resistance). There is currently no established therapy for patients who have developed resistance to PD-1/PD-L1 and platinum-doublet therapies, and novel treatments for these patients are urgently needed.

The aim of this umbrella study (D6185C00001) is to investigate multiple study drugs for the treatment of NSCLC in molecularly matched and non-matched patient populations after failure of immune checkpoint inhibitors, to identify patient populations who may respond favourably to novel anti-tumour therapies.

2.2 Background

AZD6738 (Note: per Investigator's Brochure [IB], AZD6738 is also known as ceralasertib) is currently in clinical development as an anti-cancer therapy in a variety of malignancies.

Module 11 will further investigate the contribution of components of AZD6738 monotherapy in patients with NSCLC as it is considered to be active in the combination setting with durvalumab. Background on AZD6738, including its mechanisms of action, is provided below. Detailed descriptions of the chemistry, pharmacology, efficacy, and safety of AZD6738 can be found in the IB.

Module 11 may recruit a total of up to approximately 40 patients, independent of their molecular aberration status (see Section 4.1).

2.2.1 AZD6738

2.2.1.1 Overview of AZD6738

AZD6738 is a potent, selective inhibitor of ataxia telangiectasia and Rad3-related protein (ATR), with good selectivity against other phosphatidylinositol 3-kinase-related kinase (PIKK) family members. This compound is being developed as an oral anti-tumour agent as monotherapy or in combination with the checkpoint inhibitor durvalumab (anti-PD-L1), polyadenosine 5'diphosphoribose (poly [ADP ribose]) polymerisation (PARP) inhibitors, or DNA-damaging radiotherapy or chemotherapy, in patients with DNA damage response (DDR)-deficient tumours.

ATR is a serine/threonine protein kinase and member of the PIKK family. During normal DNA replication, ATR is activated by persistent single-strand DNA breaks (SSBs) that occur if a replication fork is stalled in S-phase during DNA synthesis. Activation of ATR triggers a signal cascade leading to cell cycle arrest in S-phase whilst the DNA is repaired and the stalled replication fork resolved. Without repair, SSBs can progress to double-strand DNA breaks (DSBs), the most genotoxic form of DNA damage due to the consequences DSBs have for accurate chromosome segregation during cell division (O'Connor 2015). ATR is also recruited to single-strand DNA coated with Replication Protein A following single strand DNA damage or the resection of DSBs.

AZD6738 is an inhibitor of ATR that blocks this activity, causing stalled replication forks to collapse leading to DSBs and a dependence on ATM, a key enzyme co-ordinating the cellular response to DSBs (Weber and Ryan 2015). If the level of DNA damage exceeds the capacity to repair, nuclear fragmentation and entry into programmed cell death (apoptosis) occur (Cimprich and Cortez 2008).

ATM is a closely related kinase that is recruited to DSBs and, like ATR, has both checkpoint and repair functions. In normal cells, there is a significant interplay between ATR and ATM as stalled replication forks can be converted into DSBs through further DNA damage and the resection of DSBs generates single-stranded DNA (Stewart et al 2015; Toledo et al 2011). During tumourigenesis, ATM can be inactivated or lost providing a selection advantage for the tumour cell through the increased potential for genome alteration, and an increased dependence on ATR function. Similarly, oncogene activation such as through aberrant Myc, RAS, or cyclin D/E activity, or through tumour suppressor loss such as inactivation of ARID1A or RNA-splicing factors (transcription replication collisions) may lead to high levels of replication stress, an accumulation of stalled replication forks, and a dependence on ATR function for cancer cell survival (Forment and O'Connor 2018; Nguyen et al 2018; Williamson et al 2016).

Preclinically, AZD6738 has demonstrated antitumour activity in gastric cancer cells. In SNU-601 cells with dysfunctional ATM, AZD6738 treatment led to an accumulation of DNA

damage due to dysfunctional RAD51 foci formation, S-phase arrest, and caspase 3-dependent apoptosis, whereas SNU-484 cells with functional ATM were not sensitive to AZD6738. In addition, in an in vivo tumour xenograft mouse model, AZD6738 significantly suppressed tumour growth and increased apoptosis. These findings suggest synthetic lethality between ATR inhibition and ATM deficiency in gastric cancer cells (Min et al 2017).

2.2.1.2 AZD6738 clinical programme

Currently, for the ATR programme, there are a number of ongoing AstraZeneca sponsored clinical studies with AZD6738 in addition to HUDSON, where combinations of AZD6738 with carboplatin, olaparib or durvalumab are being explored.

In addition, Study D533BC00001 (LATIFY) will use AZD6738 plus durvalumab versus standard of care docetaxel in patients with NSCLC whose disease has progressed on or after prior anti-PD-(L)1 therapy and platinum-based chemotherapy.

A number of AstraZeneca sponsored studies incorporating AZD6738 are ongoing or completed:

- D419QC00002 study (BALTIC, NCT02937818), using AZD6738 and olaparib combination in patients with platinum refractory extensive-stage small-cell lung cancer, has completed with 21 patients dosed.
- D5336C00001 (VIOLETTE study, NCT03330847), using the AZD6738 and olaparib combination in patients with triple negative breast cancer with BRCA mutation (stratum A), HRR mutation (stratum B) and non-HRR mutation (stratum C), has completed and 109 patients were treated with AZD6738.
- Based on primary analysis in stratum A of the D5336C00001 study, D6018C00004 (DUETTE, NCT04239014), using the combination of AZD6738 and olaparib as second maintenance treatment in patients with platinum-sensitive relapsed epithelial ovarian cancer, who have previously received PARP inhibitor maintenance treatment, was terminated (no patients were randomised to treatment).
- A previous Phase I study (D5330C00001; NCT01955668) to assess multiple ascending doses of AZD6738 in patients with prospectively identified 11q-deleted relapsed/refractory chronic lymphocytic leukaemia (CLL), prolymphocytic leukaemia or B cell lymphomas was stopped after one patient was treated, due to difficulties in recruitment.
- An AstraZeneca sponsored study (D5330C00008, NCT03328273) tested AZD6738 in combination with acalabrutinib in patients with relapsed/refractory CLL; the monotherapy part of the study was discontinued due to CCI suggesting that patients had CCI with AZD6738 monotherapy, and the study was subsequently terminated early because of operational challenges impacting study execution.

- The platform study for the treatment of relapsed or refractory aggressive non-Hodgkin's lymphoma (Study D9820C00001; PRISM) recruited 2 patients in a treatment module including AZD6738 and acalabrutinib.
- Study D533AC00001 (MONETTE) is using AZD6738 as monotherapy and in combination with durvalumab in patients with unresectable or advanced melanoma who have progressed during treatment with a PD-(L)1 inhibitor ± cytotoxic T-lymphocyte associated protein 4 (CTLA-4) inhibitor.

In addition, there are Externally Sponsored Research (ESR) studies ongoing where AZD6738 is being investigated in combination with olaparib in ovarian cancer (CAPRI study [D5334C00001; NCT03462342]; results from Cohort B have been published [Shah et al 2021]) and in BAF250a (ARID1A)-deficient or BAF250a-expressing advanced solid cancers (D5330C00012; NCT03682289). Completed ERS studies include studies where AZD6738 was investigated as a single agent or in combination with radiotherapy (PATRIOT study [D5330C00002; NCT02223923]), in combination with paclitaxel (Pre-VIKTORY study [D5330C00006; NCT02630199] in patients with advanced solid tumours and enriched with metastatic melanoma [Kim et al 2021]), in combination with durvalumab (VIKTORY study [D6183C00003; NCT02299648] in patients with metastatic melanoma and gastric cancer [Lee et al 2021]), or in combination with olaparib in patients with solid tumours harbouring mutations in homology-directed repair genes (OLAPCO [D0810C00090; NCT02576444]; [Mahdi et al 2021]), in patients with relapsed small cell lung cancer (SUKSES-N2 [D5334C00003; NCT03428607]), and in triple-negative breast cancer (PlasmaMATCH Cohort E [D6184C00001; NCT03182634]).

AZD6738 monotherapy has been administered in 4 studies in addition to HUDSON:

- Study D5330C00004 (NCT02264678; solid malignancies) - 80 mg bd or 160 mg bd 21 days on and 7 days off in a 28-day cycle
- Study D5330C00008 (NCT03328273; haematological malignancies; completed) - 160 mg bd every day, and 160 mg bd from Days 1 to 14 of a 28-day cycle
- Study D5330C00007 (NCT03022409; head and neck squamous cell carcinoma [HNSCC]; completed) - 160 mg twice continuously for minimum of 10 days and maximum of 21 days
- Study D5339C00001 (PLANETTE; metastatic castration-resistant prostate cancer [mCRPC] and advanced solid tumours) Module 1 – 160 mg bd for 14 days in a 28-day cycle (dose reduced from initial starting dose of 240 mg bd for 14 days in a 28-day cycle)

See the current IB for further information.

2.2.1.3 AZD6738 monotherapy safety data

Safety data are available for AZD6738 monotherapy from Study D5330C00004 (solid malignancy), Study D5330C00008 (haematological malignancies), Study D5330C00007

(solid tumours: HNSCC) and Study D5339C00001 (ATM deficient solid tumours), and D6185C00001 (HUDSON; NSCLC) based on a data cut-off date of 13 June 2022.

The most common adverse events (AEs) (reported in > 20% of patients) for patients treated with 160 mg bd (14 days) AZD6738 monotherapy were CCI patients), CCI patients each).

The most common AEs for patients treated with 240 mg bd (14 days) AZD6738 monotherapy were CCI patients), CCI patients), and CCI patients).

CCI patients treated with 160 mg bd (14 days) AZD6738 monotherapy and CCI patients treated with 240 mg bd (14 days) AZD6738 monotherapy had CCI SAE. The most common serious adverse events (SAEs) in patients treated with 160 mg bd (14 days) AZD6738 monotherapy were CCI patients) and CCI patients). The most common SAEs in patients treated with 240 mg bd (14 days) AZD6738 monotherapy were CCI patients each). CCI treated with 240 mg bd (14 day) AZD6738 monotherapy had an SAE of CCI with an outcome of CCI that was considered by the Investigator as CCI to treatment with AZD6738.

Serious adverse reactions considered expected for safety reporting for AZD6738, either as monotherapy or various combinations, are CCI

Anaemia, thrombocytopenia, and neutropenia (including febrile neutropenia), CCI have been reported when AZD6738 is used as monotherapy and when used in combination with durvalumab.

The AEs reported for AZD6738 monotherapy are consistent with those reported for AZD6738 in combination with either carboplatin, olaparib or durvalumab, were predictable from non-clinical data and from what is known about the mechanism of action of AZD6738 and/or the underlying disease. The observed toxicities in the clinical setting have been manageable with current clinical practice. See the IB for further information.

The non-clinical and emerging safety profile has not identified any risks that would preclude investigation of AZD6738 monotherapy in the advanced cancer setting. Based on the identified and potential risks associated with treatment, this protocol incorporates mandatory safety monitoring procedures and additional guidance documents to assist with early diagnosis and rapid management of potential drug-related symptoms.

2.2.1.4 Emerging data from Module 3 and Module 8 of HUDSON and rationale for assessing AZD6738 monotherapy in Module 11

Module 3

In the current Phase II, open-label, multicentre umbrella study (D6185C00001; HUDSON) the combined effects of AZD6738 and durvalumab in overcoming immune-resistance in patients who failed PD-1/PD-L1 containing therapy are being investigated. The efficacy, safety, and tolerability of durvalumab administered in combination with AZD6738 has been investigated in both biomarker-matched (A.3.ATM) and biomarker non-matched (B.3.PRI and B.3.ACQ) patients (Module 3). From implementation of protocol version 10.0 and based on a favourable benefit-risk profile observed in Module 3, Cohorts A.3.ATM, B.3.PRI and B.3.ACQ have been re-opened for enrolment and, applicable to B.3.PRI and B.3.ACQ only, further expanded.

As of 26 October 2022, CCI patients have received AZD6738 240 mg bd plus durvalumab (7-day schedule) in Module 3 (29 patients in Cohort A.3.ATM, C in B.3.PRI, and C in B.3.ACQ). As per the data cut-off date (26 October 2022), CCI dosed patients were evaluable for response, with CCI patients still on study treatment at this time. The objective response rate (ORR) across Module 3 was CCI patients). In the A.3.ATM biomarker-matched cohort, the ORR was CCI confirmed partial responses [PRs]). In C evaluable patients a CCI disease control rate was observed at 24 weeks across Module 3 (CCI in the A.3.ATM cohort CCI evaluable]). Landmark 6, 9, and 12 months progression-free survival (PFS) and overall survival (OS) data are CCI across all cohorts, although CCI of patients in the A.3.ATM cohort are CCI the C months survival landmark, which makes it too early to conclude on survival at C months.

The safety profile of durvalumab and AZD6738 combination in HUDSON has been consistent with other ongoing studies. Of the CCI patients with safety data available on file, the most frequent (≥ 15%) AEs were reported as: CCI The most frequent (≥ 5%) Common Toxicity Criteria for Adverse Events (CTCAE) Grade ≥ 3 AE reported was CCI The most commonly reported SAE across the durvalumab/AZD6738 combination was CCI patients. The majority of SAEs reported were CCI by risk factors other than study therapy such as medical history, concurrent conditions and concomitant medications. Overall, CCI patients discontinued study treatment due to AEs, CCI of these patients discontinued treatment with AZD6738 only and CCI of these patients also discontinued durvalumab. The overall safety was as CCI criteria.

Observations made on samples taken at Cycle 0 Day 1 and Cycle 1 Day 1, representing the AZD6738 monotherapy treatment interval in Module 3 show evidence of CCI . Specifically, AZD6738 monotherapy showed statistically significant CCI HUDSON data also included significant changes in CCI potentially linked with tumour promotion.

Module 8

As of the cut-off date of 26 October 2022, C patients have received AZD6738 240 mg bd monotherapy in Module 8. The most common AEs were CCI patients), CCI patients), CCI patients), and fatigue (6/15 [40.0%] patients). The most common Grade ≥ 3 AEs were CCI patients) and CCI patients). Serious AEs possibly causally related to AZD6738 included CCI patients), CCI patients), CCI patients), CCI patients), and CCI patients); one SAE led to death; large intestinal obstruction considered unrelated to AZD6738.

These HUDSON data provide CCI of similar data from the AZD6738 Study D5330C00004. Taken together, these clinical datasets provide compelling evidence that AZD6738 monotherapy CCI . These data confirm a role for AZD6738 CCI within this post-anti-PD(L)-1 population.

Based on emerging clinical, safety and translational data, findings would suggest exploring AZD6738 monotherapy to further investigate the contribution of components CCI in patients who have failed prior PD-1/PD-L1 containing therapy.

2.3 Benefit/risk assessment

As described in Section 2.3 of the core protocol, patients recruited to this study are not expected to have other treatment options apart from monotherapy chemotherapy, such as docetaxel. The survival outcome and toxicity profile of chemotherapy in this setting mean that other active therapies are highly desirable and present a potential advantage for patients.

The study design aims to identify patient populations who may respond favourably to novel anti-tumour therapies. Based upon the available non-clinical and clinical safety data, the limited survival benefit provided by the currently available treatment options to patients, and the limited life expectancy due to malignant disease, the investigation of the potential therapeutic efficacy of AZD6738 monotherapy in patients with advanced or metastatic NSCLC is acceptable, and the overall benefit/risk assessment supports the proposed study design.

3. OBJECTIVES AND ENDPOINTS

Please refer to the core protocol.

4. STUDY DESIGN

4.1 Overall design

This is an open-label, multi-centre, umbrella study in patients who have received an anti-PD-1/PD-L1 containing therapy and a platinum-doublet regimen for locally advanced or metastatic NSCLC either separately or in combination. The patient must have had disease progression on a prior line of anti-PD-1/PD-L1 therapy. For an overview of the study design see Figure 1; further details on the overall design are provided in Section 4 of the core protocol. For details on the study treatments given in Module 11, see Section 6.1.

Module 11 (HUDSON)

Module 11 (Group C; molecular aberration independent) will evaluate the efficacy, safety, and tolerability of AZD6738 monotherapy (240 mg bd given orally) in NSCLC patients, independent of their molecular aberration status. Up to approximately 40 patients may be assigned to a single cohort to receive AZD6738 240 mg bd (Cohort C.11.240). Enrolment to Module 11 will be sequential such that recruitment will be prioritised once Module 10 in Group C is complete.

Patients will be defined by prior response to immunotherapy; primary resistance or acquired resistance. These terms are defined as follows:

- Primary resistance; patients who had anti-PD-1/PD-L1 containing therapy but had progression of disease (PD) within ≤24 weeks from the start of treatment.
- Acquired resistance; patients who had progressive disease >24 weeks from the start of anti-PD-1/PD-L1 containing therapy whilst still on that treatment.

For the patient allocation process, see Section 4.1.4 (Clinical Screening Procedures) of the core protocol.

A study flow diagram is provided in the core protocol (Figure 4).

4.2 Scientific rationale for study design

The study aims to identify patient populations who may respond favourably to novel anti-tumour therapies, and the modular design allows evaluation of the efficacy, safety, and tolerability of multiple study drugs. The study requires an open-label design owing to the different schedules and routes of administration of the study drugs.

Module 11 will enrol patients, independent of their molecular aberration status, to investigate the contribution of components of AZD6738 monotherapy in NSCLC, as it is considered to be active in the combination setting with durvalumab.

4.3 Justification for AZD6738 dose

The dose of AZD6738 as monotherapy for this module is 240 mg bd from Day 1 to Day 7 of every 28-day cycle. In Study D533BC00001 (LATIFY), AZD6738 at 240 mg bd will be dosed from CCI followed by durvalumab 1500 mg on Day C of each 28-day cycle. This 240 mg dose has also been used as monotherapy and in combination with durvalumab 1500 mg administered on Day 1 of each 28-day cycle in Module 3 of Study D5330C00004 (NCT02264678), where a total of C patients have been treated. In Cohort 5 investigating AZD6738 240 mg bd 7 days in combination with durvalumab 1500 mg, 7 patients were treated; in Cohort 6 and the expansion cohort investigating AZD6738 240 mg bd 14 days in combination with durvalumab 1500 mg, a total of C patients have been treated (data cut-off 21 February 2022). Both dose regimens were CCI and 240 mg bd 14 days was later declared – after initiation of the HUDSON study (D6185C00001) –as the recommended Phase II dose.

Preliminary safety data has shown that AZD6738 240 mg bd from CCI of every 28-day cycle is CCI as monotherapy as well as in combination with durvalumab (Study D5330C00004; data on file). Population pharmacokinetic (PK) model simulations showed that the dose of 240 mg bd for C days is predicted to CCI the percentage of patients CCI having an optimal cycle cover, defined as the time in which plasma concentrations of AZD6738 are maintained above the in vitro CCI per cycle, of CCI hours. The target of 182 hours is based on preclinical data and is considered optimal to achieve maximum tumour regression under AZD6738 monotherapy. In addition, one-week AZD6738 dosing CCI T-cell proliferative burst during the CCI period, potentially promoting upregulation of PD-L1 which can be subsequently blocked with durvalumab to enhance anti-tumour T-cell responses.

The dose level of 240 mg bd is predicted to CCI AZD6738 concentrations CCI the estimated concentration of an inhibitor where ATR catalytic activity is reduced by CCI threshold for C hours in CCI of patients (data on file). A sigmoid model links AZD6738 monotherapy exposure with the difference between CCI and CCI

Based on the aforementioned data, the use of AZD6738 240 mg bd as monotherapy from Day 1 to Day 7 of every 28-day cycle in this module is justified.

Furthermore, considering emerging PK data from ongoing studies, there is CCI

4.4 End of study definition

Please refer to the core protocol.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study in order to be assigned to a study cohort. Under no circumstances can there be exceptions to this rule. Patients who do not meet the entry requirements are screen failures; refer to Section 5.4 of the core protocol.

5.1 Inclusion criteria (Module 11-specific)

Patients are eligible to be included in the study only if all the following inclusion criteria apply. Please also refer to the Section 5.1 of the core protocol for the inclusion criteria applicable to all modules in the study. Additional inclusion criteria applicable to Module 11 only are described in this section.

S-1 Patients must fulfil all the core eligibility criteria.

S-2 Washout of prior immunotherapy of ≥ 28 days.

5.2 Exclusion criteria (Module 11-specific)

Patients must not enter Module 11 of the study if any of the following exclusion criteria apply. Refer to Section 5.2 of the core protocol for the exclusion criteria applicable to all modules in the study.

Additional exclusion criteria applicable to Module 11 only are described below:

Medical conditions

S-1 Patients whose tumour samples have known targetable alterations in EGFR and/or ALK, ROS1, BRAF, MET or RET at initial diagnosis are excluded. In addition, patients whose tumour samples are identified to have targetable alterations in EGFR, ALK, ROS1, BRAF, MET or RET prior to study enrolment will need the Investigator to confirm interest in enrolling the patient in the study with the sponsor. If targeted alterations are detected retrospectively in central test results, the Investigator should assess benefit of ongoing treatment (as specified in the core protocol, Section 7.3).

S-2 Diagnosis of ataxia telangiectasia.

S-3 Refractory nausea and vomiting, chronic gastrointestinal diseases or previous significant bowel resection, with clinically significant sequelae that would preclude adequate absorption of AZD6738.

S-4 Inadequate bone marrow reserve or organ function as demonstrated by any of the following laboratory values: absolute neutrophil count < 1.5 x 10^9/L; platelet count < 100 x 10^9/L; haemoglobin < 90 g/L, with no blood transfusion (packed red blood cells) in the past 28 days.

S-5 Persisting (> 4 weeks) severe pancytopenia due to previous therapy rather than disease (absolute neutrophil count [ANC] < 1.5 x 10^9/L or platelets < 100 x 10^9/L).

S-6 Creatinine clearance < 40 mL/min calculated by Cockcroft-Gault equation (see Table 5 in the core protocol for the calculation).

S-7 Haematuria: +++ on microscopy or dipstick.

S-8 International normalised ratio (INR) ≥ 1.5 or other evidence of impaired hepatic synthesis function.

S-9 Alkaline phosphatase > 2.5 x upper limit of normal (ULN) (and liver disease unrelated to the tumour). Patients with elevated alkaline phosphatase (ALP) due to tumour related bone metastases or liver metastases will be eligible.

S-10 Patients with relative hypotension (< 100/60 mmHg) or clinically relevant orthostatic hypotension, including a fall in blood pressure of > 20 mmHg.

Prior/concomitant therapy

S-11 Concomitant use of known strong CYP3A inhibitors (eg, itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir). The required washout period prior to starting study intervention is 2 weeks.

S-12 Concomitant use of known strong CYP3A inducers (eg, phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort). The required washout period prior to starting study intervention is 5 weeks for enzalutamide or phenobarbital and 3 weeks for other agents.

S-13 Prior exposure to an ATR inhibitor.

S-14 Concomitant use of proton pump inhibitors (eg, omeprazole, pantoprazole). AZD6738 exhibits pH-dependent solubility; therefore, the use of acid-reducing agents may affect its bioavailability. H2 antagonists (eg, ranitidine) and antacids (eg, bismuth subsalicylate) can be used to relieve symptoms of gastro-oesophageal hyperacidity but should be administered in a staggered manner with respect to AZD6738 dosing (a few hours either before or after intake of AZD6738).

Other

S-15 Inability to swallow the formulated product.

For procedures for withdrawal of incorrectly enrolled patients see Section 7.3 of the core protocol.

5.3 Lifestyle restrictions

Please refer to Section 5.3 of the core protocol for contraception requirements.

5.4 Screen failures

Please refer to the core protocol.

6. STUDY TREATMENTS

Study treatment is defined as any study drug(s) (including marketed product comparator and placebo) or medical device(s) intended to be administered to a study participant according to the study protocol. Study treatment in Module 11 refers to AZD6738 monotherapy.

6.1 Treatments administered

6.1.1 Study drugs

Table 2 Study drugs

	AZD6738
Dosage formulation:	Oral tablets in either 20, 80 or 100 mg
Route of administration:	Oral
Dosing instructions:	240 mg twice daily for 7 days on treatment in each 28-day cycle, between Days 1 and 7.
Packaging and labelling	Study drug will be provided in high-density polyethylene bottles with child-resistant closures. Labels will be prepared in accordance with GMP and local regulatory guidelines. Label text will be translated into local language, as required. AZD6738 will be provided with either single-panel labels or multi-language booklet labels. Specific dosing instructions will not be included on the label; the site must complete the "Patient Dispensing Card" with the details of the dosing instructions at the time of dispensing. The Investigator's emergency contact details will not be on the label but can be found in the informed consent and the 'Patient Dispensing Card'. For emergency purposes the patient must be in possession of the emergency contact details at all times.
Provider	AstraZeneca

GMP = Good Manufacturing Practice

6.2 Preparation/handling/storage/accountability

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study drugs received and any discrepancies are reported and resolved before use of the study drug.

Only patients enrolled in the study may receive study drugs and only authorised site staff may supply or administer study drugs. All study drugs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the Investigator and authorised site staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study drugs accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study drug are provided in the Pharmacy Manual.

6.2.1 Study drug administration

When AZD6738 is administered, patients must fast (water to drink only) for at least 2 hours prior to taking a dose, to at least 1-hour post-dose for all doses.

AZD6738 will be administered orally 240 mg bd, approximately 12 hours apart, starting on Day 1 until Day 7 of each treatment cycle, starting with Cycle 1. Patients must receive AZD6738 for 7 days within a 28-day cycle. A cycle must not be < 28 days. AZD6738 must not be given on any other days of the cycle, and dosing days must stay relative to Day 1 of each cycle. In case of drug interruption within the planned Day 1 to 7 dosing window (for any reason), resumption of treatment can only take place within the planned dosing window and not beyond, even if this means the subject receives less than the specified 7 days AZD6738 dosing in the particular cycle. The planned 21 days off treatment should not be reduced.

Patients are allowed to take the scheduled dose up to 2 hours after the scheduled dose time. If greater than 2 hours, the missed dose should not be taken and the patient should continue with the next dose at the allotted time. If the patient wishes to bring forward the time of their scheduled dose, the dose can be taken up to a maximum of 2 hours prior to the scheduled time, ie, ± 2-hour window.

Patients should continue to receive study treatment until objective radiological disease progression as per Response Evaluation Criteria in Solid Tumours (RECIST 1.1), as long as, in the Investigator’s opinion, they are benefiting from treatment and they do not meet any other discontinuation criteria. Disease progression should be confirmed by a subsequent scan (no earlier than 4 weeks later) in the absence of clinically significant deterioration as assessed

by the Investigator. All patients who have objective progression of disease will enter follow-up.

There will be an option for patients with progressive disease on AZD6738 monotherapy (progression must be confirmed as per RECIST) to have durvalumab added on their AZD6738 treatment, for as long as this is considered in the patient's best interest by the Investigator, and with approval of the sponsor. As the combination treatment durvalumab + AZD6738 is still a non-approved therapy, this will need to be considered as study medication and will require safety assessments accordingly (see Section 6.7). Note, this is **not** to be considered as a re-allocation to Module 10.

6.2.2 Storage

All study drugs should be kept in a secure place under appropriate storage conditions.

The AZD6738 product label on the bottle specifies the appropriate storage.

The study drug must be kept in the original outer container and under conditions specified on the labels.

In the following cases, the centre staff should not use affected study drug and should immediately contact the AstraZeneca representative for further guidance:

- Temperature excursion upon receipt or during storage at the study
- Damaged kit upon receipt
- Damaged bottle

Damaged study drug should be documented according to the instructions provided by the AstraZeneca representative. Storage conditions stated in the IB, or the study drug Handling Instructions document, may be superseded by the label storage.

6.2.3 Accountability

The study drugs provided for this study should only be used as directed in the study protocol.

The study site staff will account for all study drugs received at the centre, for unused study drugs, and for appropriate destruction (according to local procedures). Certificates of delivery, destruction, and/or return should be signed.

The administration of all medications (including study drug) and details of treatment with study drug should be recorded in the appropriate sections of the electronic Case Report Form (eCRF).

6.3 Measures to minimise bias: randomisation and blinding

This is an open-label study.

If a patient withdraws from participation in the study, then his/her enrolment code cannot be reused. Withdrawn patients will not be replaced.

6.4 Treatment compliance

The administration of all study drugs should be recorded in the appropriate sections of the eCRF. Treatment compliance will be assured by reconciliation of site drug accountability logs. Patients will record their oral AZD6738 dosing on a diary which should be returned to the site at the next available visit. Sites should additionally record AZD6738 doses taken at site visits.

Patients will self-administer AZD6738. Patients should be given clear instructions on how and when to take their study treatment. Study site staff will make tablet counts at regular intervals during treatment when the bottles are returned per cycle. Compliance will be assessed by the tablet count and the information will be recorded in the appropriate section of the eCRF. After the tablet count has been performed, the remaining tablets will not be returned to the patient but will be retained by the investigative site until reconciliation is completed by the study monitor. All patients must return their bottle(s) of AZD6738 at the appropriate scheduled visit, when a new bottle will be dispensed. Patients will be instructed to notify study site personnel of missed doses. Dates of missed or held doses will be recorded by the patient on their patient diary and by the site staff on the eCRF.

Patients must return all containers and any remaining tablets at their next scheduled treatment cycle and at the end of the study.

Any change from the dosing schedule, dose interruptions, dose reductions, dose discontinuations should be recorded in the eCRF.

The Study Drug Storage Manager is responsible for managing the study drug from receipt by the study site until the destruction or return of all unused study drug. The Investigator(s) is/are responsible for ensuring that the patient has returned all unused study drug.

Use of study treatment in doses in excess of that specified in the protocol is considered to be an overdose. Refer to Section 8.4.3 in the core protocol for procedures in case of overdose.

6.5 Concomitant therapy

Any medication or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the patient is receiving at the time of enrolment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Prohibited concomitant medications are described in Table 3. Please refer to Section 8.4.5 for guidance on management of study drug-related toxicities.

The use of concomitant medications must be recorded in the eCRF.

Table 3 Prohibited medications

Prohibited medication/class of drug	
Unless stated otherwise, these medications are prohibited from the time that patients enter the main screening period until the last dose of study treatment. The pre-screen may be done whilst on prior therapy.	
Any investigational anticancer therapy other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment
Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment. (Note: concurrent use of hormones for non-cancer-related conditions [eg, insulin for diabetes and hormone replacement therapy] is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable [eg, by local surgery or radiotherapy]). Patients may receive treatment with bisphosphonates or RANKL inhibitors for the treatment of bone metastases
Immunosuppressive medications, including, but not limited to: systemic corticosteroids at doses exceeding 10 mg/day of prednisone or its equivalent, methotrexate, azathioprine, and tumour necrosis factor-α blockers	Should not be given concomitantly, or used for premedication prior to the infusions. The following are allowed exceptions: • Use of immunosuppressive medications for the management of study drug-related AEs • Short-term premedication for patients receiving combinations where the prescribing information for the agent requires the use of steroids for documented hypersensitivity reactions • Use in patients with contrast allergies • In addition, use of inhaled, topical, and intranasal corticosteroids is permitted. A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of non-immunotherapy related events experienced by the patient (eg, chronic obstructive pulmonary disease, radiation, nausea, etc).
Live attenuated vaccines	Prohibited from the time that patients enter the main screening period until 180 days after the last dose of study treatment.
Herbal and natural remedies which may have immune-modulating effects	Should not be given concomitantly unless agreed by the Sponsor

AE = adverse event; RANKL = receptor activator of nuclear factor kappa-B ligand.

The use of herbal preparations/medications should be discouraged throughout the study. These herbal medications include, but are not limited to: St. John's Wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone, yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 7 days prior to the first dose of study drug (3 weeks for

St John's Wort). Use of these products, as well as use of all vitamins, nutritional supplements and all prescribed concomitant medications, must be recorded in the eCRF.

Other concomitant treatment

Medication other than that described above, which is considered necessary for the patient's safety and wellbeing, may be given at the discretion of the Investigator and recorded in the appropriate sections of the eCRF.

6.5.1 Rescue and supportive medication

There is no rescue medication for AZD6738 monotherapy.

Supportive medication, described in Table 4, may be given at the discretion of the Investigator and recorded in the appropriate sections of the eCRF.

Table 4 Supportive medication

Supportive medication/class of drug	Usage
Concomitant medications or treatments (eg, acetaminophen or diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care, except for those medications identified as "prohibited," as listed above	To be administered as prescribed by the Investigator
Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy to non-target lesions, etc])	Should be used, when necessary, for all patients AZD6738 treatment should be discontinued for a minimum of 3 days before a patient undergoes palliative radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.
Inactivated viruses, such as those in the influenza vaccine or authorised and approved COVID-19 vaccines.	Permitted. Administration of COVID-19 vaccines should be avoided for 72 hours prior to administration of the first dose of study treatment.

COVID-19 = Coronavirus Disease 2019.

6.5.2 Drug-drug interaction between AZD6738 and other drugs

AZD6738 is an investigational drug for which no data on in vivo interactions are currently available. Potential interaction and guidelines below are considered on the basis of preclinical in vitro data only.

The lists of CYP and transporter inhibitors/inducers, and CYP and transporter substrates are available in Section 11. They are not exhaustive and the absence of a drug from these lists

does not imply that its combination with AZD6738 is safe. If AZD6738 is being administered in combination, potential interactions of the combination partner should also be considered.

- **Restrictions regarding drugs affecting CYP metabolism**
  The principal enzyme for metabolising AZD6738 is CYP[CCI]. Patients should avoid concomitant drugs, herbal supplements, and/or ingestion of foods known to modulate CYP[CCI] activity from the time they enter the screening period until 28 days after the last dose of study medication.
  - Prior to study medication, use of potent inducers or inhibitors of CYP[CC] are not permitted. For patients taking any of these drugs, the required wash-out periods before starting AZD6738 is five half-lives; except for St. John's wort, which is 3 weeks.
  - On study medication, if there is no suitable alternative concomitant medication other than a potent inhibitor of CYP[CCI] the Investigator must interrupt AZD6738 for the duration of the potent CYP[CC] inhibitor and wait for the required wash-out period (five half-lives) before dosing AZD6738 again. If potent CYP[CC] inducers are considered necessary for the patient's safety and welfare, this may diminish the clinical efficacy of AZD6738, and the patient should be monitored carefully for any change in the efficacy of study treatment. Refer to Section 11 for additional guidance.
  - The use of any herbal supplements or 'folk remedies' (and medications and foods that significantly modulate CYP[CC] activity) should be discouraged. If deemed necessary, such products may be administered with caution and the reason for use documented in the eCRF.

In vitro data also suggest that AZD6738 may be metabolised by CYP[CCI] to a lesser extent, therefore caution should be applied with co-administration of potent inhibitors or inducers of CYP[CCI] (examples provided in Section 11).

- **Drugs known to be inhibitors or inducers of [CCI] undertake appropriate monitoring if co-administration is necessary**
  - AZD6738 is also a [CCI] substrate. Co-administration of [CCI] inhibitors or inducers may affect exposure to AZD6738 and therefore should not be co-administered with AZD6738. If the use of any inhibitors or inducers of [CCI] are considered necessary for the patient's safety and welfare, the Investigator must interrupt AZD6738 for the duration of the [CCI] inhibitor or inducer and wait for the required wash-out period of the [CCI] modulator (5 half-lives) before dosing with AZD6738.
  - AZD6738 is a substrate of [CCI] Co-administration of [CCI] inhibitors or inducers may affect exposure to AZD6738; therefore, it is recommended that the Investigators must interrupt AZD6738 for the duration of the [CCI] inhibitor or inducer and wait

for the required wash-out period of the CCI modulator (5 half-lives) before dosing AZD6738 again.

- **Drugs known to be substrates of CYPCCI and/or CYPCCI CYPCCI and CYPCCI undertake appropriate monitoring if coadministration is necessary**
  - AZD6738 is an inducer of CYPCCI CYPCCI and CYPCCI and showed weak inhibition of CYPCCI CYPCCI and CYPCCI Caution should be applied with co-administration of drugs that are either completely metabolised by CYPCCI and/or CYPCCI CYPCCI or CYPCCI or that are substrates of CYPCCI and/or CYPCCI CYPCCI and CYPCCI and also have a narrow therapeutic index. Investigators should be aware that the exposure of other drugs metabolised by CYPCCI CYPCCI and/or CYPCCI may be increased, and exposure of other drugs metabolised by CYPCCI and/or CYPCCI may be reduced.

- **Drugs known to be substrates of CCI undertake appropriate monitoring if co-administration is necessary**
  - AZD6738 is an inhibitor of CCI Co-administration of substrates of CCI may affect exposure to AZD6738; therefore, it is recommended that caution should be applied when such drugs are to be administered with AZD6738.

- **Anticoagulation therapy**
  - Patients on warfarin may participate in this study but it is recommended that their INR is monitored more frequently.

6.6 Dose modification and discontinuation

Dose adjustments for AZD6738 will be based on the organ system exhibiting the greatest degree of toxicity. All toxicities will be graded according to CTCAE version 4.03. Dose reductions or interruptions, and initiation of supportive care, are allowed as deemed appropriate by the treating physician. The maximum interruption or cycle delay that is permitted is 28 days.

Management of study drug-related toxicities is described in detail in Section 8.4.5.

Table 5 AZD6738 dose modifications for toxicity management (7-day schedule)

Dose level	AZD6738
Initial dose	240 mg twice daily Days 1-7
Level 1 dose reduction	160 mg twice daily Days 1-7
Level 2 dose reduction	160 mg once daily Days 1-7

Table 5 AZD6738 dose modifications for toxicity management (7-day schedule)

Dose level	AZD6738
Level 3 dose reduction	Stop treatment

Study treatment dose interruption for conditions other than toxicity resolution should be kept as short as possible. If a patient cannot restart study treatment within 4 weeks of the planned onset date, for resolution of intercurrent conditions not related to disease progression or toxicity, the case should be discussed with the AstraZeneca study physician. Any patient requiring a toxicity related dose delay of more than 28 days from the planned onset of AZD6738 must be discontinued from the study treatment unless there is approval from the study physician for the patient to continue.

All dose reductions and interruptions (including any missed doses), and the reasons for the reductions/interruptions are to be recorded in the eCRF.

Study treatment should be stopped at least 3 days prior to planned surgery. After surgery study treatment can be restarted when the wound has healed. No stoppage of study treatment is required for any biopsy procedure.

Patients who develop an event of ≥ Grade 3 of thrombocytopenia, anaemia, and/or neutropenia later than Cycle 2 in their treatment will need to have additional assessment on Day 8 (± 1 day window) until there is no evidence of ≥ Grade 3 thrombocytopenia, anaemia, and/or neutropenia for at least 2 cycles.

6.7 Treatment after the end of the study

Patients are permitted to either receive standard of care therapy, or to continue to receive study treatment following the end of the study if, in the opinion of the Investigator, they are continuing to receive benefit from treatment. After discontinuation of study treatment, the Investigator will be at liberty to define further most appropriate anti-cancer treatment. Subsequent anti-cancer treatment is expected to be initiated following the cancer recurrence or development of a new cancer. Information on subsequent anti-cancer therapies should be recorded on the clinical database.

For details on planned assessments and the treatment schedule (and dose modification guidelines) of the combination of durvalumab and AZD6738 post disease progression, see Table 6 and dose modification guidelines in the core protocol. This combination treatment will follow the Schedule of Assessment as described in Table 6, until the time of the final data cut-off (DCO, please refer to section 4.4 of core protocol for further details).

When switching to combination treatment, one of the following scenarios may apply:

- **If the patient can start the combination treatment immediately after the end of monotherapy**: The first dose of durvalumab must be administered on the day after completion of a full 7-day course of AZD6738.
- **If the patient cannot start the combination treatment immediately after the end of monotherapy**: The combination treatment should begin no earlier than 21 days after the last dose of AZD6738 monotherapy, starting with a further 7-day course of AZD6738 (C0) as described in Table 6.

After final DCO, each patient still receiving the combination of durvalumab and AZD6738 post disease progression will be switched to standard of care for clinical management and will be followed-up by the local investigator according to standard local clinical practice. After final DCO, all investigators will continue to report all SAEs using paper forms (please refer to Section 8.4.1 of core protocol for further details).

This combination treatment will need to be reconsidered when last OS follow-up has taken place for the monotherapy setting of Module 11. Further arrangements will be determined by the overall actions taken for patients on trial at that moment.

Dosing instructions:

- AZD6738 (oral): 240 mg bd (or the dosing regimen that the patient was on at the time of ending monotherapy, if different) with 7 days on treatment in each cycle between Days 22 and 28.
- Durvalumab (IV infusion): Patients enrolled in the study will receive 1500 mg via intravenous infusion every 4 weeks (Q4W) +2 days (fixed dosing for patients >30 kg body weight).

Table 6 Schedule of Activities – Combination of AZD6738 + Durvalumab After the end of Module 11 monotherapy

	Cycle 0[d, e] 7-day lead-in	**C1**[f] 28 days Weeks 1-4		**C2** 28 days Weeks 5-8		**C3 - etc** All cycles 28 days	**Study drug disc.** (28 days after study drug disc.)	**Safety follow-up** (90 days after study drug disc.)	**Survival follow-up**	**Notes**
Week	**-1**	**1**	**4**	**5**	**8**	**9, 13, 17, etc**				
Day of cycle	**1**	**1**	**22**	**1**	**22**	**1**				
Window (days)		**±2**	**±2**	**±2**	**±2**	**±2**	**±7**	**±7**	**±7**	
Study procedures[b]										

	Cycle 0[d, e] 7-day lead-in	**C1**[f] 28 days Weeks 1-4		**C2** 28 days Weeks 5-8		**C3 - etc** All cycles 28 days	**Study drug disc.** (28 days after study drug disc.)	**Safety follow-up** (90 days after study drug disc.)	**Survival follow-up**	**Notes**
Week	**-1**	**1**	**4**	**5**	**8**	**9, 13, 17, etc**				
Day of cycle	**1**	**1**	**22**	**1**	**22**	**1**				
Window (days)		**±2**	**±2**	**±2**	**±2**	**±2**	**±7**	**±7**	**±7**	
Physical examination	X	X		X		X	X			Section 8.2.2 (core protocol)
Vital signs[a]	X	X		X		X	X			Section 8.2.3 (core protocol)
ECG	X	X		X		X				Section 8.2.4 (core protocol)
Concomitant medications	X	X		X		X	X			Section 6.5
Laboratory assessments[b]										
Clinical chemistry	X	X	X[g]	X	X[g]	X	X			Section 8.2.1 (core protocol). If screening laboratory assessments are performed within 3 days prior to Day 1 they do not need to be repeated
Haematology[c]	X	X	X[g]	X	X[g]	X	X			
APTT and INR	As clinically indicated									
TSH, free T_3 and free T_4	X	X		X		X	X			Section 8.2.1 (core protocol)
Urinalysis	As clinically indicated									Section 8.2.1 (core protocol)
Pregnancy test	X	X		X		X	X			Section 8.2.1.2 (core protocol)
AE/SAE	X	X		X		X	X	X		Section 8.3 (core protocol)

	Cycle 0[d, e] 7-day lead-in	**C1**[f] 28 days Weeks 1-4		**C2** 28 days Weeks 5-8		**C3 - etc** All cycles 28 days	**Study drug disc.** (28 days after study drug disc.)	**Safety follow-up** (90 days after study drug disc.)	**Survival follow-up**	**Notes**
Week	**-1**	**1**	**4**	**5**	**8**	**9, 13, 17, etc**				
Day of cycle	**1**	**1**	**22**	**1**	**22**	**1**				
Window (days)		**±2**	**±2**	**±2**	**±2**	**±2**	**±7**	**±7**	**±7**	
Study drug administration[b]										
Durvalumab		X[h]		X[h]		X[h]				Section 6.2.1
AZD6738	X Days 1-7		X Days 22-28		X Days 22-28	X Days 22-28				Section 6.1.1
Drug accountability	X	X		X		X	X			Section 6.2.3
Other assessments										
Tumour evaluation (CT or MRI, RECIST 1.1)			RECIST assessment frequency should be maintained as it was when AZD6738 monotherapy was discontinued							Section 8.1 (core protocol)

[a] If clinically indicated, blood pressure to be measured in the supine and standing positions after at least 10 minutes' rest.

[b] Following the final data cut-off for final analysis, for patients who do continue to receive treatment beyond the time of the final data cut-off, investigators will continue to report all SAEs, pregnancy, and overdose until 90 days after the last dose of study treatment, in accordance with Section 8.4.1 of the core CSP using paper forms. Additionally, in accordance with Section 4.4 of the core CSP, any SAE that is ongoing at the time of the final data cut-off must be followed up to resolution unless the event is considered by the investigator to be unlikely to resolve, or the patient is lost to follow-up.

[c] Eosinophil, monocyte, lymphocyte, and neutrophil counts will be recorded for patients as part of the routine white blood cell count for safety assessment.

[d] If the patient cannot start the combination therapy directly after the seven days of monotherapy (C1D1), the schedule of study drug administration of the post-progression combination therapy should begin no earlier than 21 days from the last dose of AZD6738 of the monotherapy with another 7-day course of AZD6738 (C0).

[e] If C0D1 visit coincides with the end of treatment visit of the monotherapy, the safety assessments should not be repeated.

[f] If the patient can start the combination treatment immediately after the end of monotherapy, the safety assessments performed as part of the monotherapy end of treatment should not be repeated.

[g] Haematology and clinical chemistry assessments will take place on Day 22 (± 2-day window) of Cycles 1 and 2. If any toxicity is detected during these additional safety assessments, the patient will be managed as per the protocol, and as clinically indicated. If a patient has an event of thrombocytopenia, anaemia and/or neutropenia that is ≥ Grade 3 during the first 2 cycles, this additional safety assessment will be included in subsequent cycles until there is no evidence of ≥ Grade 3 thrombocytopenia, anaemia, and/or neutropenia for at least 2 cycles.

[h] +3-day window.

AE adverse event; APTT activated partial thromboplastin time; C cycle; CSP clinical study protocol; CT computed tomography; ECG electrocardiogram; INR international normalised ratio; RECIST 1.1 Response Evaluation Criteria in Solid Tumours 1.1; MRI magnetic resonance imaging; Q12W every 12 weeks; Q24W every 24 weeks; SAE serious adverse event; TSH thyroid-stimulating hormone; T_3 triiodothyronine; T_4 thyroxine.

7. DISCONTINUATION OF TREATMENT AND PATIENT WITHDRAWAL

Please refer to Section 7 in the core protocol. Stopping criteria for AZD6738 are in Section 8.4.5 of this module.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in the SoA (Table 1).

8.1 Efficacy assessments

Please refer to the core protocol.

8.2 Safety assessments

8.2.1 Clinical safety laboratory assessments

Please refer to core protocol.

8.2.1.1 Coagulation

Please refer to core protocol.

8.2.1.2 Other safety assessments

Please refer to core protocol.

8.2.1.3 Pneumonitis (interstitial lung disease) investigation

The following assessments, and additional assessments if required, will be performed to enhance the investigation and diagnosis of potential cases of pneumonitis. The results of the assessment will be collected.

- Physical examination; Signs and symptoms (cough, shortness of breath and pyrexia, etc) including auscultation for lung field will be assessed.
- Saturation of peripheral oxygen (SpO_2)
- Other items; When pneumonitis (interstitial lung disease [ILD]) is suspected during study treatment, the following markers should be measured where possible:
  - ILD markers (KL-6, SP-D) and β-D-glucan
  - Tumour markers: Particular tumour markers which are related to disease progression.

8.2.2 Physical examinations

Please refer to core protocol.

8.2.3 Vital signs

Please refer to Section 8.2.3 in the core protocol. However, if clinically indicated, eg, in the event of clinically relevant symptoms such as pre-syncope or dizziness, blood pressure will be measured in the supine and standing positions after at least 10 minutes' rest. Assessments will be performed at the visits as shown in the SoA (Table 1).

8.2.4 Electrocardiograms

Please refer to core protocol.

8.2.5 Performance status

Please refer to core protocol.

8.3 Collection of adverse events

Please refer to the core protocol.

8.4 Safety reporting and medical management

8.4.1 Reporting of serious adverse events

Please refer to the core protocol.

Any myeloid malignancies (ie., MDS and/or AML) should be reported whenever this has been observed in the follow-up of the patients.

8.4.2 Pregnancy

Please refer to the core protocol.

8.4.3 Overdose

Please refer to the core protocol.

8.4.4 Medication error

Please refer to the core protocol.

8.4.5 Management of study drug-related toxicities

If a patient experiences a clinically significant and/or unacceptable toxicity, dosing will be interrupted and supportive therapy administered as required.

If the toxicity resolves or reverts to CTCAE Grade ≤ 1 or 2 (depending on the toxicity), treatment with AZD6738 may be restarted using the rules in Table 7 for dose modifications. Patients who are at the lowest possible dose, or who had their dose previously reduced to the lowest possible dose and who have demonstrated an acceptable response to the dose

interruption may be permitted to restart at the lowest dose level at the discretion of the Investigator.

If the toxicity does not resolve to CTCAE Grade ≤ 1 or 2 or the patient is not showing clinical benefit, then the patient should be discontinued from treatment and observed until resolution of the toxicity.

Any patient requiring a toxicity related dose delay of more than 28 days from the planned onset of AZD6738 must be discontinued from the study treatment unless there is approval from the study physician for the patient to continue.

If a patient develops severe haematologic toxicity or blood transfusion dependence, treatment with AZD6738 should be interrupted and appropriate haematologic testing should be initiated. If the blood parameters remain clinically abnormal after 4 weeks of AZD6738 dose interruption, bone marrow analysis and/or blood cytogenetic analysis are recommended. If myeloid malignancies are confirmed whilst on treatment with AZD6738, it is recommended that AZD6738 should be discontinued and the patient be treated appropriately. AEs of myeloid malignancies should be monitored by conventional AE collection and reporting, additionally any cases should be reported after the 30-day follow-up period irrespective of Investigator causality.

The dose of AZD6738 must not be adjusted under any other circumstances than those described in this section unless prior agreement is given by the Sponsor.

All dose modifications and interruptions (including any missed doses) and the reasons for the modifications/interruptions are to be recorded in the eCRF.

Table 7 Dose interruption and stopping criteria (7-day schedule)

Event	Action
Grade 1-2 toxicities (except Grade 2 neutropenia and thrombocytopenia)	AZD6738 dosing may continue with supportive treatment (as required) or Investigator decision whether to interrupt AZD6738 (maximum 28 days). Following interruption, AZD6738 may be resumed at the same dose level.
Grade 2 neutropenia or Grade 3 anaemia	Blood counts may recover during the “off drug period” on the intermittent schedule. AZD6738 dosing may continue with supportive treatment (as required eg, transfusion) or Investigator decision whether to interrupt AZD6738 (maximum 28 days). Following interruption, AZD6738 may be resumed at the same dose level or dose reduced by 1 level[a].

Table 7 Dose interruption and stopping criteria (7-day schedule)

Event	Action
Grade 2-3 thrombocytopenia	**First occurrence** Interrupt AZD6738 (maximum 28 days) until platelets improve to ≥75,000/mm^3. Following interruption, AZD6738 may be resumed at the same dose level, as blood counts may recover during the "off period" on the intermittent schedule. If blood counts do not recover by the start of the next dosing period, AZD6738 should be restarted with a dose reduction by 1 level[a]. **Subsequent occurrences** Interrupt AZD6738 (maximum 28 days) until platelets improve to ≥75,000/mm^3. Following interruption, AZD6738 should be restarted with a dose reduction by 1 level[a].
Grade 4 thrombocytopenia	Interrupt AZD6738 (maximum 28 days) and give appropriate supportive treatment until platelets improve to ≥75,000/mm^3. Following interruption, AZD6738 should be restarted with a dose reduction by 1 level[a].
Grade 3-4 toxicity (including Grade 3-4 neutropenia or Grade 4 anaemia) *Excludes* Grade 3 anaemia or Grade 3-4 thrombocytopenia (see above)	**First occurrence** Interrupt AZD6738 (maximum 28 days) and give appropriate supportive treatment. When toxicity has resolved to grade 1, AZD6738 should be restarted with a dose reduction by 1 level[a]. **Subsequent occurrences** Investigator discretion on whether to interrupt AZD6738 (maximum 28 days) or to stop treatment. Following interruption, AZD6738 should be restarted with a dose reduction of 1 or 2 levels.
Vomiting	If vomiting occurs shortly after AZD6738 is swallowed, the dose should only be replaced if all of the intact tablets can be counted. Resume with the following scheduled dose.
Missed dose	Allowed to take the scheduled dose up to 2 hours after the scheduled dose time. If greater than 2 hours, the missed dose should not be taken and the patient should continue with next dose at the allotted time.

[a] This table is for guidance. Therefore, for example, it may be deemed appropriate by the Investigator to reduce the dose by more than 1 dose level depending on the individual patient circumstances.

Individual stopping criteria:

Hepatic

- ALT or AST or ALP* > 5 × ULN
- ALT or AST or ALP* > 3 × ULN with the appearance of symptoms associated with a clinical diagnosis of hepatitis including right upper quadrant pain or tenderness, fever, rash or eosinophilia (> 5%)
- [ALT or AST > 3 × ULN] and [total bilirubin > 2 × ULN or INR$^+$ >1.5 or other evidence of impairment to the synthesis function of the liver]

* In the presence of bone metastasis, assess bone specific isoform of raised ALP in the presence of a raised gamma-glutamyltransferase (to ensure the ALP change is specific to the liver).
\+ Unless patient is receiving warfarin.

Please refer to Appendix E of the core protocol "Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law".

Cardiovascular

Clinically significant hypotension defined as an asymptomatic decrease of more than 20 mmHg in systolic blood pressure to below 70 mmHg persisting for at least 10 minutes.

Symptomatic orthostatic fall in systolic blood pressure of more than 20 mmHg compared to resting supine systolic blood pressure.

Haematologic

Patients with suspected or with indications of MDS and/or AML must have the dose of AZD6738 stopped under all circumstances, and evidence of AML/MDS should be ruled out. Further treatment can only be accepted after discussion and agreement with the sponsor.

8.5 Pharmacokinetics

Not applicable for this module.

8.6 Pharmacodynamics

Pharmacodynamic parameters will be evaluated in this study (see Section 8.6 of the core protocol).

8.7 Genetics

Refer to the core protocol.

8.8 Biomarkers

Refer to the core protocol. Note, whole blood samples for flow cytometry will be collected for up to 20 patients in Module 11 and only if a sample has been collected at screening.

8.9 Medical Resource Utilisation and Health Economics

Medical Resource Utilisation and Health Economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

Refer to the core protocol for general statistical considerations.

Specifically for the safety analysis in Module 11, the following should be considered:

For patients who receive AZD6738 monotherapy and who do not go on to receive durvalumab + AZD6738 combination as subsequent therapy:

- A treatment-emergent adverse event (TEAE) is defined as an event with an onset date or worsening in CTCAE grade on or after the date of first dose of AZD6738 and up to and including 90 days following the date of last dose of AZD6738.

For patients who discontinue AZD6738 monotherapy and go on to receive durvalumab + AZD6738 combination as subsequent therapy:

- A TEAE is defined as any AE that started or worsened in CTCAE grade on or after the first dose of AZD6738 monotherapy, until 90 days follow-up after discontinuation of AZD6738 monotherapy, unless the investigator assesses the relatedness of the AE with onset during this interval to the AZD6738 from the durvalumab + AZD6738 combination.

Any AE occurring within the defined 90-day follow-up period after discontinuation of AZD6738 monotherapy, except for those with onset during this interval for which the investigator assesses the relatedness to the AZD6738 therapy from the durvalumab + AZD6738 combination, will be included in the AE summaries. AEs occurring after the 90-day follow-up period after discontinuation of study drug, and AEs with onset during the defined 90-day follow-up period after discontinuation of study drug from AZD6738 monotherapy for which the investigator assesses the relatedness of the AE to the AZD6738 therapy from the durvalumab + AZD6738 combination, will be listed separately, but not included in the summaries.

10. REFERENCES

Cimprich and Cortez 2008
Cimprich KA, Cortez D. ATR: an essential regulator of genome integrity. Nat Rev Mol Cell Biol. 2008;9(8):616-27.

Forment and O'Connor 2018
Forment JV, O'Connor MJ. Targeting the replication stress response in cancer. Pharmacol Ther. 2018;188:155-67.

Kim et al 2021
Kim ST, Smith SA, Mortimer P, Loembé A-B, Cho H, Kim K-M, et al. Phase I study of ceralasertib (AZD6738), a novel DNA damage repair agent, in combination with weekly paclitaxel in refractory cancer. Clin Cancer Res. 2021;27(17):4700-9.

Lee et al 2021
Lee J, Kim ST, Kim K, Lee H, Kozarewa I, Mortimer PGS et al. Tumor genomic profiling guides patients with metastatic gastric cancer to targeted treatment: The VIKTORY umbrella trial. Cancer Discov. 2019 Oct;9(10):1388-405.

Mahdi et al 2021
Mahdi H, Hafez N, Doroshow D, Sohal D, Keedy V, Do KT, et al. Ceralasertib-mediated ATR inhibition combined with olaparib in advanced cancers harboring DNA damage response and repair alterations (olaparib combinations). JCO Precis Oncol. 2021;5:PO.20.00439.

Min et al 2017
Min A, Im S-A, Jang H, Kim S, Lee M, Kim DK et al. AZD6738, A Novel Oral Inhibitor of ATR, Induces Synthetic Lethality with ATM Deficiency in Gastric Cancer Cells. Mol Cancer Ther. 2017;16(4);566–77.

Nguyen et al 2018
Nguyen HD, Leong WY, Li W, Reddy PNG, Sullivan JD, Walter MJ, et al. Spliceosome mutations induce R loop-associated sensitivity to ATR inhibition in myelodysplastic syndromes. Cancer Res. 2018;78(18):5363-74.

O'Connor 2015
O'Connor MJ. Targeting the DNA Damage Response in Cancer. Mol Cell. 2015;60(4):547-60.

Shah et al 2021
Shah PD, Wethington SL, Pagan C, Latif N, Tanyi J, Martin LP, et al. Combination ATR and PARP Inhibitor (CAPRI): A phase 2 study of ceralasertib plus olaparib in patients with recurrent, platinum-resistant epithelial ovarian cancer. Gynecol Oncol. 2021;163(2):246-253.

Stewart et al 2015
Stewart R, Morrow M, Hammond SA, Mulgrew K, Marcus D, Poon E, et al. Identification and characterization of MEDI4736, an antagonistic anti-PD-L1 monoclonal antibody. Cancer Immunol Res. 2015;3(9):1052-62.

Toledo et al 2011
Toledo LI, Murga M, Zur R, Soria R, Rodriguez A, Martinez S et al. A cell-based screen identifies ATR inhibitors with synthetic lethal properties for cancer-associated mutations. Nat Struct Mol Biol. 2011;18(6):721-7.

Weber and Ryan 2015
Weber AM, Ryan AJ. ATM and ATR as therapeutic targets in cancer. Pharmacol Ther. 2015;149:124-38.

Williamson et al 2016
Williamson CT, Miller R, Pemberton HN, Jones SE, Campbell J, Konde A, et al. ATR inhibitors as a synthetic lethal therapy for tumours deficient in ARID1A. Nat Commun. 2016;7:13837.

11. AZD6738 DRUG-DRUG INTERACTIONS

Restrictions regarding drugs affecting CYP[CC] metabolism

There are currently no data confirming that there is a pharmacokinetic (PK) interaction between drugs that affect CYP[CC] metabolism and AZD6738; a potential interaction is considered on the basis of preclinical and in vitro data only. AZD6738 is predominantly eliminated via CYP[CC] metabolism, therefore CYP[CC] inhibitors or inducers may increase or decrease exposure to AZD6738, respectively. Potent inhibitors or inducers of CYP[CC] should not be combined with AZD6738. In vitro data also suggest that AZD6738 may be metabolised by CYP[CCI] to a lesser extent, therefore caution should be applied with co-administration of potent inhibitors or inducers of CYP[CCI]

Drugs known to be inhibitors and inducers of CYP[CC] or CYP[CCI] are listed in Table 8 and Table 9, respectively. These lists are not intended to be exhaustive, and similar restrictions will apply to other agents that are known to modulate CYP[CC] or CYP[CCI] activity. Please contact AstraZeneca with any queries on this issue. Please refer to full prescribing information for all drugs prior to co-administration with AZD6738.

Table 8 Drugs known to be inhibitors and inducers of CYP[redacted]

Potent CYP[redacted] inhibitors	Potent CYP[redacted] inducers
boceprevir	apalutamide
ceritinib	avasimibe
clarithromycin	carbamazepine
cobicistat (GS-9350)	ceralasertib
conivaptan	enzalutamide
danoprevir / RIT	ivosidenib
elvitegravir / RIT	lumacaftor
grapefruit juice[a]	mitotane
idelalisib	phenobarbital
indinavir	phenytoin
indinavir /RIT	rifampin
itraconazole	rifapentine
ketoconazole	St John's Wort extract
LCL161	
lopinavir / RIT	
mibefradil	
mifepristone	
nefazodone	
nelfinavir	
posaconazole	
ribociclib	
ritonavir	
saquinavir	
saquinavir / RIT	
telaprevir	
telithromycin	
tipranavir/RIT	
troleandomycin	
VIEKIRA PAK2[b]	
voriconazole	

[a] Double-strength grapefruit juice. Patients should abstain from eating large amounts of grapefruit and Seville oranges (and other products containing these fruits eg, grapefruit juice or marmalade) during the study (eg, no more than a small glass of grapefruit juice (120 mL) or half a grapefruit or 1 to 2 teaspoons (15 g) of Seville orange marmalade daily.

[b] VIEKIRA PAK = 150/100 mg paritaprevir/ritonavir + 25 mg ombitasvir + 800 mg dasabuvir for 28 days.

List created using the University of Washington Drug-Drug Interaction Database July 2019.
RIT = Ritonivir. Ritonavir has dual effects of simultaneous CYP[redacted] inhibition and induction, and the net pharmacokinetic outcome during chronic ritonavir therapy is inhibition of CYP[redacted] activity

Table 9 Drugs known to be inhibitors and inducers of CYP[CCI]

Potent CYP2C8 inhibitors	Potent CYP[CCI] inducers
gemfibrozil clopidogrel	None identified

List created using the University of Washington Drug-Drug Interaction Database Jan 2020.

Drugs known to be inhibitors or inducers of [CCI] undertake appropriate monitoring if co-administration is necessary

AZD6738 is a substrate of [CCI] Co-administration of [CCI] inhibitors/inducers or [CCI] inhibitors/inducers may affect exposure to AZD6738, therefore it is recommended that these are not co-administered with AZD6738.

Drugs known to be inhibitors or inducers of [CCI] are listed in Table 10 and Table 11, respectively. These lists are not intended to be exhaustive, and similar restrictions will apply to other agents that are known to modulate [CCI]. Please contact AstraZeneca with any queries on this issue. Please refer to full prescribing information for all drugs prior to co-administration with AZD6738.

Table 10 Drugs known to be inhibitors or inducers of [CCI]

Drugs Known to be Inhibitors of [CCI]	Drugs Known to be Inducers of [CCI]
alogliptin	apalutamide
amiodarone	avasimibe
asian ginseng (Panax ginseng)	carbamazepine
asunaprevir	danshen (Salvia miltiorrhiza)
AZD5672	efavirenz
azithromycin	genistein
canagliflozin	green tea
captopril	phenytoin
carvedilol	quercetin
clarithromycin	rifabutin
clopidogrel	rifampin
cobicstat	ritonavir
conivaptan	St. John's wort extract
cremophor EL	tivantinib
cremophor RH	
curcumin	
daclatasvir	
daclatasvir/asunaprevir/beclabuvir	
diltiazem	
diosmin	

dronedarone	
elagolix	
eliglustat	
erythromycin	
felodipine	
five-flavor berry (schisandra chinensis)	
flibanserin	
fluvoxamine	
fostamatinib	
ginkgo	
glecaprevir/pibrentasvir	
indinavir	
indinavir/ritonavir	
isavuconazole	
itraconazole	
ivacaftor	
ketoconazole	
lapatinib	
lopinavir/ritonavir	
mibefradil	
mifepristone	
milk thistle	
mirabegron	
nelfinavir	
neratinib	
nifedipine	
nitrendipine	
osimertinib	
paritaprevir/ritonavir/ombitasvir	
paroxetine	
piperine	
propafenone	
quercetin	
quinidine	
quinine	
ranolazine	
rifampin	
ritonavir	
rolapitant	
rucaparib	
saquinavir/ritonavir	
sarecycline	

simeprevir	
sofosbuvir/velpatasvir/voxilaprevir	
St. John's wort extract	
surfactant TPGS	
suvorexant	
talinolol	
telithromycin	
telaprevir	
telmisartan	
tezacaftor/ivacaftor	
ticagrelor	
tipranavir/ritonavir	
tolvaptan	
valbenazine	
valspodar (PSC 833)	
vandetanib	
velpatasvir	
vemurafenib	
verapamil	
voclosporin	
vorapaxar	

List created using the University of Washington Drug-Drug Interaction Database October 2019.

Table 11 Drugs known to be inhibitors or inducers of CCI

Drugs Known to be Inhibitors of CCI	Drugs Known to be inducers of CCI
afatinib	Please check individual drugs on a case-by-case basis
aripiprazole	
curcumin	
cyclosporine	
elacridar	
erlotinib	
fluvastatin	
fumitremorgin	
gefitinib	
ivermectin	
lapatinib	
nilotinib	
novobiocin	
pantoprazole	
pitavastatin	
ponatinib	
quercetin	

quizartinib	
rabeprazole	
regorafenib	
rilpivirine	
sulfasalazine	
sunitinib	
tacrolimus	
teriflunomide	
trametinib	
trifluoperazine	
vismodegib	
eltrombopag	
atazanavir	
lopinavir	
ritonavir	
tipranavir	
omeprazole	
estrone	
17b-estradiol	
imatinib mesylate	

List created using http://dmd.aspetjournals.org/content/dmd/43/4/490.full.pdf
Note: Although CCI is involved in a number of clinically relevant DDIs, none of the listed inhibitors above is truly specific for this transporter

Drugs known to be substrates of CYPCCI and/or CYPCCI or CYPCCI or CYPCCI undertake appropriate monitoring if co-administration is necessary

AZD6738 is an inducer of CYPCCI CYPCCI and CYPCCI and showed weak inhibition of CYPCCI CYPCCI and CYPCCI Therefore, caution should be applied with co-administration of drugs that are either completely metabolised by CYPCCI and/or CYPCCI or CYPCCI or CYPCCI or that are substrates of CYPCCI and/or CYPCCI CYPCCI and CYPCCI and also have a narrow therapeutic index (Table 12). Investigators should be aware that the exposure of other drugs metabolised by CYPCCI CYPCCI and/or CYPCCI may be increased, and exposure of other drugs metabolised by CYPCCI and/or CYPCCI may be reduced.

Table 12 Drugs known to be metabolised by CYPCCI and/or CYPCCI CYPCCI and CYPCCI

Metabolised by CYPCCI	Metabolised by CYPCCI	Metabolised by CYPCCI	Metabolised by CYPCCI
Abemaciclib (NTR)	agomelatine	daprodustat	benzbromarone
ABT-384	alosetron[a]	dasabuvir	celecoxib
Acalabrutinib (NTR)	caffeine	repaglinide[b]	ibuprofen
alfentanil	duloxetine		(R)-ibuprofen

alisporivir almorexant alpha-dihydroergocryptine aplaviroc aprepitant asunaprevir atazanavir atorvastatin avanafil avapritinib AZD1305 BIRL 355 blonanserin bosutinib (NTR) brecanavir brotizolam budesonide buspirone BZF961 capravirine casopitant cobimetinib (NTR) conivaptan (NTR) danoprevir darifenacin darunavir dasatinib (NTR) dronedarone ebastine eletriptan eliglustat (in subjects CYP CCI PMs) elvitegravir entrectinib (NTR) eplerenone everolimus felodipine ibrutinib indinavir isavuconazole itacitinib ivabradine	melatonin pirfenidone ramelteon[a] selegiline[a] tacrine tasimelteon[a] tizanidine (NTR)		(S)-ibuprofen glimepiride glipizide lornoxicam meloxicam piroxicam (S)-warfarin (NTR) tolbutamide

ivacaftor L-771,688 Levomethadyl/Levacetymethadol (LAAM) (NTR) Lomitapide (NTR) lonafarnib lopinavir lovastatin lumefantrine lurasidone maraviroc midazolam midostaurin (NTR) morphothiadin naloxegol neratinib (NTR) nisoldipine paritaprevir4 perospirone pyrotinib quetiapine ridaforolimus saquinavir sildenafil simeprevir simvastatin sirolimus tacrolimus terfenadine ticagrelor tilidine3 tipranavir tolvaptan (NTR) triazolam ubrogepant ulipristal vardenafil venetoclax (NTR) vicriviroc vilaprisan voclosporin zanubrutinib (NTR)			

[a] Complex Interaction -Substrates metabolized by multiple enzymes, including CYP[CCI]
[b] Repaglinide is also a substrate of [CCI] which might also be inhibited by gemfibrozil or its glucuronide.
List created using the University of Washington Drug-Drug Interaction Database August 2021. Note: This is not an exhaustive list.
(NTR) drug listed in the Narrow Therapeutic Index list by CYP isoform in DrugBank.

Drugs known to be substrates of [CCI] undertake appropriate monitoring if co-administration is necessary

AZD6738 is also an inhibitor of [CCI] Caution should be applied with co-administration of substrates of [CCI] as AZD6738 may increase their exposure.

Drugs known to be substrates of [CCI] are listed in Table 13 and Table 14, respectively. These lists are not intended to be exhaustive and appropriate medical judgment is required. Please contact AstraZeneca with any queries on this issue. Please refer to full prescribing information for all drugs prior to co-administration with AZD6738.

Table 13 Drugs known to be substrates of [CCI]

docetaxel
enalapril
olmesartan
phalloidin
repaglinide
statins[a]
temocaprilat
valsartan

[a] All statins
List created using https://www.solvobiotech.com/transporters/[CCI] latest access Nov 2019

Table 14 Drugs known to be substrates of [CCI]

anthracyclines
chlorothiazide
daunorubicin
doxorubicin
imatinib
irinotecan
methotrexate
mitoxantrone
nucleoside analogues
pantoprazole
prazosin

SN-38
topotecan
teriflunomide
rosuvastatin

List created using https://www.solvobiotech.com/transporters[redacted] latest access Nov 2019.

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