MONETTE: A Randomised, Open-Label, Phase 2 Study of Ceralasertib Monotherapy and Ceralasertib plus Durvalumab in Patients with Unresectable or Advanced Melanoma and Primary or Secondary Resistance to PD-(L)1 Inhibition

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MONETTE: A Randomised, Open-Label, Phase 2 Study of Ceralasertib Monotherapy and Ceralasertib plus Durvalumab in Patients with Unresectable or Advanced Melanoma and Primary or Secondary Resistance to PD-(L)1 Inhibition

Sponsor Name: AstraZeneca AB

Legal Registered Address: AstraZeneca AB, S-151 85 Södertälje, Sweden

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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.

Protocol Number: D533AC00001

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Study Treatment: Ceralasertib monotherapy or ceralasertib plus durvalumab

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Short Title: MONETTE: A Phase 2 Study of Ceralasertib Monotherapy and Ceralasertib Plus Durvalumab in Patients with Unresectable or Advanced Melanoma and Resistance to PD-(L)1 Inhibition

Acronym: MONETTE

Study clinical lead: AstraZeneca study physician name and contact information will be provided separately

International co-ordinating investigator: PPD
PPD
PPD
PPD

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 3	17-December-2024
Amendment 2	14-March-2022
Amendment 1	01-July-2021
Original Protocol	13-May-2021

Amendment 3

This modification is considered to be substantial based on the criteria set forth in Regulation (EU) No 536/2014 of the European Parliament.

Overall Rationale for the Amendment:

The clinical study protocol (CSP) Amendment 2, dated 14-March-2022, has been updated to include new Reference Safety Information in line with the Investigator's Brochure (IB) update and clarification has been added for the planned safety data collection in the Post-trial Access Program. Further, the duration of contraception after the last dose of study treatment was updated to align with the Sponsor's drug safety recommendations. In addition, requirements from the EU Regulation No 536/2014 were consolidated into the global protocol to create a single, unified document. Minor formatting and editorial corrections are not presented in this summary.

Summary of Changes:

List of Substantial Modifications

Section Number and Name	Description of Change	Brief Rationale
Section 2.3.1 Risk Assessment Table 4 Risk Assessment	In the description of risks associated with ceralasertib treatment, fatigue/asthenia were added to the list of identified risks and MDS/AML were added to the list of potential risks.	To align with ceralasertib IB, edition 13, dated 18 September 2024. Selection criteria were not required to be updated in the context of these risks because the study is no longer recruiting patients.
AML = acute myeloid leukaemia; IB = Investigator's Brochure; MDS = myelodysplastic syndrome.		

List of Non-Substantial Modifications

Section Number and Name	Description of Change	Brief Rationale
Cover Page	EU CT Number added on the CSP cover page.	To comply with EU-CTR requirement.
Section 1.1 Synopsis; Section 1.3 Schedule of Activities; Section 5.1.1 Inclusion Criteria; Section 5.2.1 Exclusion Criteria; Section 5.3.1 Contraception; Section 7.1.2 Follow-up of Patients Post Discontinuation of Study Treatment; Section 8.3.13.2 Paternal Exposure	The new appendix, Appendix K1.1, was cross-referenced to indicate country-specific requirements for Belgium.	For document navigation.
Section 1.1 Synopsis; Section 1.3 Schedule of Activities; Section 4.1 Overall Design; Section 5.1.1 Inclusion Criteria; Section 5.2.1 Exclusion Criteria; Section 5.3.1 Contraception; Section 6.6 Dose Modification; Section 7.1 Discontinuation of Study Treatment; Section 7.1.2 Follow-up of Patients Post Discontinuation of Study Treatment; Section 8.3.13.2 Paternal Exposure	The new appendix, Appendix K1.2, was cross-referenced to indicate country-specific requirements for France.	For document navigation.
Section 1.1 Synopsis; Section 4.1 Overall Design; Section 8.3 Adverse Events and Serious Adverse Events; Section 9.2.1 Sample Size Determination; Appendix A3 Informed Consent Process; Appendix G Guidelines for Evaluation of Objective Tumour Response Using RECIST 1.1 (Response Evaluation Criteria in Solid Tumours)	The new appendix, Appendix K1.3, was cross-referenced to indicate country-specific requirements for Germany.	For document navigation.
Section 1.1 Synopsis Section 7.1.2 Follow-up of Patients Post Discontinuation of Study Treatment	Corrected time period of follow-up for safety assessments post treatment discontinuation from “90 days” to “180 days” after last dose of study treatment for ceralasertib and durvalumab combination.	Correction.

Section Number and Name	Description of Change	Brief Rationale
Section 4.4 End of Study Definition	Clarified definition of the end of study according to EU and FDA requirements.	For consistency and alignment in terms of posting study results.
Section 5.1.1 Inclusion Criteria, Main Study and Biopsy Sub-Study; Section 5.3.1 Contraception	Updated the contraception period after the last dose of study intervention for female patients from 1 month to 6 months. Added a restriction that female patients must not breastfeed and must not donate or retrieve ova from signing the ICF to approximately 6 months after the last dose of study treatment.	To align with the latest safety outcomes and recommendations for contraception.
Section 6.5.2 Drug-Drug Interaction Between Ceralasertib and Other Drugs; Appendix F Guidelines Regarding Potential Interactions of Ceralasertib with Concomitant Medications, including the table listing drugs known to be metabolised by CCI [redacted]	Addition of ceralasertib as a potential inducer of CCI [redacted].	To align with the current ceralasertib IB, edition 13, dated 18 September 2024.
Section 6.6.1 Management of Toxicities	Added guidance on management of prolonged haematological toxicities	To align with Sponsor's guidance ceralasertib toxicity management updated consequence to including MDS/AML as potential risks.
Section 6.7 Treatment After the End of the Study; Section 8.3.1 Time Period and Frequency for Collecting AE and SAE information	Added wording related to PTAP.	To clarify the planned safety data collection and reporting during the PTAP.
Section 8.3.7 Disease Progression	Added text on reporting of disease progression as a safety event in applicable cases.	For clarification.
Section 8.3.11 Safety Data to be Collected Following the Final Data Cutoff of the Study	Updated wording for safety data reporting.	For clarifying procedure for data collection.
Section 8.3.12 Reporting of Serious Adverse Events	Addition of wording to describe reporting of SUSARs to the EudraVigilance Database, in accordance with EU-CTR 536/2014.	Update required to comply with regulatory requirement (eg, EU-CTR).

Section Number and Name	Description of Change	Brief Rationale
Section 8.3.12 Reporting of Serious Adverse Events	Added wording for SAE reporting.	For clarifying procedure for data collection.
Section 8.3.13.1 Maternal exposure	Added wording for pregnancy related reporting.	For clarifying procedure for data collection.
Section 8.3.14 Medication Error, Drug Abuse, and Drug Misuse	Updated common wording for reporting standards.	To align with the latest CSP template.
Section 8.3.14 Medication Error	Added Drug Abuse and Drug Misuse definition. The level 3 heading was changed to "Medication Error, Drug Abuse, and Drug Misuse".	To comply with EU guidance on the collection, verification, and presentation of safety data from clinical trials and with Sponsor's corporate safety standards.
Section 8.4 Overdose	Added wording regarding AE/SAE reporting in case of overdose.	To align with the latest CSP template.
Section A 1 Regulatory and Ethical Considerations	Updated regulatory reporting Requirements for SAEs.	To comply with EU Regulation No. 536/2014.
Appendix A1	Added sub-heading "Regulatory Reporting Requirements for Serious Breaches of Protocol or GCP".	To comply with regulatory requirement (eg, EU-CTR) and global company requirement.
Appendix A4	Updated Data Protection information and added sub-heading "Personal Data Breaches".	To comply with EU-CTR.
Appendix A6	Updated information about timelines for submission of study results summaries to EMA.	To comply with EU-CTR.
Appendix A7	Updated template wording and added information about retention timelines of records and documents to "25 years after study archiving or as required by local regulations".	To comply with EU-CTR and to align with Sponsor's company policy.
Appendix B4	Added detailed Drug Abuse and Drug Misuse definition and examples.	To comply with EU guidance on the collection, verification and presentation of safety data from clinical trials and with Sponsor's corporate safety standards.
Appendix J Abbreviations	List of abbreviations updated.	To define newly added abbreviations.

Section Number and Name	Description of Change	Brief Rationale
Appendix K Country-specific Requirements	Added new Appendix to allow for consolidation of country-specific CSPs.	To consolidate local CSP amendments for Belgium, France, and Germany into a single, as required per EU-CTR.
AE = adverse event; CSP = clinical study protocol; CTR = Clinical Trials Regulation; EMA = European Medicines Agency; EU = European Union; EU-CTR = European Union Clinical Trials Regulation; FDA = Food and Drug Administration; GCP = good clinical practice; IB = Investigator's Brochure; ICF = Informed Consent Form; PTAP = Post-trial Access Program; SAE = serious adverse event; SUSAR = suspected unexpected serious adverse reaction.		

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: MONETTE: A Randomised, Open-Label, Phase 2 Study of Ceralasertib Monotherapy and Ceralasertib plus Durvalumab in Patients with Unresectable or Advanced Melanoma and Primary or Secondary Resistance to PD-(L)1 inhibition

Short Title: MONETTE: A Phase 2 Study of Ceralasertib Monotherapy and Ceralasertib Plus Durvalumab in Patients with Unresectable or Advanced Melanoma and Resistance to PD-(L)1 Inhibition

Rationale: This Phase 2 study aims to evaluate the efficacy and safety/tolerability of ceralasertib, when administered as monotherapy and in combination with durvalumab in patients with unresectable or advanced melanoma and primary or secondary resistance to PD-(L)1 inhibition. The rationale for conducting the study is supported by clinical data from ongoing studies, unmet need, and the evidence of ceralasertib modulating the immune environment.

An open-label, non-randomised, biopsy sub-study is also planned in patients suitable for 3 mandatory biopsies. The rationale for conducting the biopsy sub-study is to understand the mechanism of action of ceralasertib plus durvalumab and investigate ceralasertib as an immune modulator.

Objectives and Endpoints

Objectives	Endpoints
Main Study	
Primary	
• To estimate the effectiveness of ceralasertib monotherapy and ceralasertib plus durvalumab by assessment of objective response rate (ORR) in patients with unresectable or advanced melanoma and primary or secondary resistance to a PD-(L)1 inhibitor	• The primary measure is the estimate of ORR for each experimental treatment arm, and a secondary measure of interest is the odds ratio of the ORR comparing the 2 treatment arms
Secondary	
• To estimate the effectiveness of ceralasertib monotherapy and ceralasertib plus durvalumab by assessment of Duration of Response (DoR) in patients with unresectable or advanced melanoma and primary or secondary resistance to a PD-(L)1 inhibitor	• Median and landmark DoR estimates at 6, 9, 12, 15, and 18 months
• To estimate the effectiveness of ceralasertib monotherapy and ceralasertib plus durvalumab by assessment of time to objective response (TTR) in patients with unresectable or advanced melanoma and primary or secondary resistance to a PD-(L)1 inhibitor	• Median TTR and proportion of patients with response at the first scheduled tumour assessment
• To estimate the effectiveness of ceralasertib monotherapy and ceralasertib plus durvalumab by assessment of change in target lesion (TL) tumour size in patients with unresectable or advanced melanoma and primary or secondary resistance to a PD-(L)1 inhibitor	• Percentage change from baseline in TL tumour size at week 16 and best percentage changes from baseline
• To estimate the effectiveness of ceralasertib monotherapy and ceralasertib plus durvalumab by assessment of progression free survival (PFS) in patients with unresectable or advanced melanoma and primary or secondary resistance to a PD-(L)1 inhibitor	• Median and landmark PFS at 3, 6, 9, 12 months, and the hazard ratio comparing the 2 treatment arms
• To estimate the effectiveness of ceralasertib monotherapy and ceralasertib plus durvalumab by assessment of overall survival (OS) in patients with unresectable or advanced melanoma and primary or secondary resistance to a PD-(L)1 inhibitor	• Median and landmark OS at 6, 9, 12, and 18 months, and the hazard ratio comparing the 2 treatment arms
• To assess the PK of ceralasertib alone and when in combination with durvalumab	• Concentration of ceralasertib in plasma (peak and trough concentrations, as data allow; sparse sampling)
Safety	
• To assess the safety and tolerability of ceralasertib monotherapy and ceralasertib plus durvalumab in patients with unresectable or advanced melanoma and primary or secondary resistance to a PD-(L)1 inhibitor	• Safety and tolerability will be evaluated in terms of adverse events (AEs), vital signs, and clinical laboratory assessments.

Objectives	Endpoints
Exploratory objectives	
• CCI [redacted]	• CCI [redacted] • CCI [redacted]
• CCI [redacted]	• CCI [redacted]
• CCI [redacted]	• CCI [redacted]
• CCI [redacted]	• CCI [redacted]
• CCI [redacted]	• CCI [redacted]

Objectives	Endpoints
• CCI [redacted]	• CCI [redacted]
• CCI [redacted]	• CCI [redacted]
• CCI [redacted]	• CCI [redacted]
Biopsy Sub-Study	
Primary	
• To assess changes in CD8+ T-cell infiltration of tumours induced by ceralasertib monotherapy	• CD8+ T-cells tumour infiltration assessed in baseline, on-treatment and off-treatment tumour biopsies

Objectives	Endpoints
Secondary	
• To estimate the effectiveness of ceralasertib plus durvalumab by assessment of ORR, DoR, TTR, change in tumour size, PFS, and OS	• As described for the main study
• To collect tumour tissue samples, or utilise residual samples, for the analysis of tumoural biomarkers that change following treatment with ceralasertib	• Pre-treatment presence and/or on-treatment and/or off-treatment changes in PD-L1 and pRAD50
• To assess changes in the proliferation of carcinoma and/or immune cells within tumours induced by ceralasertib monotherapy	• Proliferation (using Ki67+ marker) of carcinoma and/or immune cells (including CD8+ T cells) will be assessed in baseline, on-treatment and off-treatment tumour biopsies.
Safety	
• To assess the safety and tolerability of ceralasertib plus durvalumab in patients with unresectable or advanced melanoma and primary or secondary resistance to a PD-(L)1 inhibitor	• As described for the main study
Exploratory	
• CCI [redacted]	• CCI [redacted]
• CCI [redacted]	• CCI [redacted]

Objectives	Endpoints
• CCI [redacted]	• CCI [redacted]
• CCI [redacted]	• CCI [redacted]

Overall Design

This is a Phase 2, randomised, open-label study of ceralasertib monotherapy and ceralasertib plus durvalumab in patients with unresectable or advanced melanoma and primary or secondary resistance to PD-(L)1 inhibition. Patients will be recruited from multiple centres with a global footprint that is expected to include North America, Europe, and Asia.

An open-label, non-randomised, biopsy sub-study is planned in patients suitable for 3 mandatory biopsies. Patients recruited into the biopsy sub-study will receive 1 cycle of ceralasertib monotherapy (Cycle 0) followed by ceralasertib plus durvalumab from Cycle 1.

Disclosure Statement:

This is a Phase 2, randomised, open-label, multicentre, international study assessing the efficacy and safety of ceralasertib monotherapy and ceralasertib plus durvalumab in patients with unresectable or advanced melanoma with resistance to PD-(L)1 inhibition.

Patient Population:

The target population of interest in this study is patients with unresectable or advanced melanoma, measurable by RECIST 1.1, with confirmed progression during treatment with a PD-(L)1 inhibitor +/- a CTLA-4 inhibitor, eg, nivolumab, pembrolizumab, or atezolizumab, or the combination of nivolumab and ipilimumab, and with availability of a mandatory fresh tumour biopsy (if medically feasible) and a mandatory archival tumour sample of up to 5 years, at screening.

Number of Patients:

Main study: Approximately 150 patients are expected to be randomised in total, at a 2:1 randomisation ratio, such that there will be approximately 100 evaluable patients in the ceralasertib and durvalumab combination therapy arm and approximately 50 patients in the ceralasertib monotherapy arm. However, fewer patients may be randomised to any given treatment arm following a recommendation by the Independent Data Monitoring Committee (IDMC) to terminate recruitment to an arm based on safety or lack of efficacy.

Enrolled	Estimated CCI patients
Randomly assigned	Estimated 150 patients
Evaluable patients	Estimated 150 patients

Biopsy sub-study:

The estimated number of patients in the biopsy sub-study is as follows:

Enrolled	Estimated CCI patients
Evaluable tumour biopsy patients	Estimated 30 patients

Note: "Enrolled" means a patient's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential patients who are screened for the purpose of determining eligibility for the study, but are not randomised/assigned in the study, are considered "screen failures", unless otherwise specified by the protocol. For country-specific requirements for Germany see Appendix K 1.3.

Treatment Groups and Duration:

Main study: The treatment arms are as follows:

- **Arm 1:** Ceralasertib 240 mg BD, oral tablets, from Days 1 to 7, plus durvalumab 1500 mg Day 8, IV infusion, Q28D, until progressive disease (confirmed RECIST 1.1-defined radiological progression), unacceptable toxicity, withdrawal of consent, or if a study treatment discontinuation criterion is met.
- **Arm 2:** Ceralasertib 240 mg BD, oral tablets, from Days 1 to 7, Q28D, until progressive disease (confirmed RECIST 1.1-defined radiological progression), unacceptable toxicity, withdrawal of consent, or if a study treatment discontinuation criterion is met.

There is no defined maximum treatment duration for the treatment arms as the patients will receive study treatment until progressive disease (confirmed RECIST 1.1-defined radiological progression), unacceptable toxicity, withdrawal of consent, or if a study treatment discontinuation criterion is met.

Randomization into the treatment arms will be stratified by:

- Resistance to prior immune-oncology treatment (primary/early relapse in adjuvant setting vs secondary resistance).
- Baseline lactate dehydrogenase expression (below and equal to the upper limit of normal vs above upper limit of normal).

Biopsy sub-study: During Cycle 0, patients will be treated with ceralasertib 240 mg BD, as oral tablets, from Days 1 to 7, Q28D, followed by an off-treatment period between Days 8 to 28. From Cycle 1, patients will be treated with the combination of ceralasertib 240 mg BD, oral tablets, from Days 1 to 7, plus durvalumab 1500 mg Day 8, as an IV infusion, Q28D, until progressive disease (confirmed RECIST 1.1-defined radiological progression), unacceptable toxicity, withdrawal of consent, or if a study treatment discontinuation criterion is met.

Follow-up of patients post discontinuation of study treatment for main and biopsy sub-study: After study treatment discontinuation, all patients will be followed up for safety assessments 30 days after their last dose of study treatment for ceralasertib monotherapy or 180 days after last dose of study treatment for ceralasertib and durvalumab combination (ie, the safety follow-up visit). All randomised patients in the main study and all patients in the biopsy sub-study will be followed for survival status and post discontinuation anti-cancer therapies. For country-specific requirements for Belgium and France see Appendices K 1.1 and K 1.2 respectively.

Patients who have discontinued study treatment in the absence of Response Evaluation Criteria in Solid Tumours (RECIST) 1.1-defined (per investigator assessment) radiological progression will be followed up with tumour assessments according to the Schedule of Activities (SoA) until RECIST 1.1-defined disease progression or death (whichever comes first) regardless of whether or not the patient started a subsequent anti-cancer therapy, unless they have withdrawn all consent to study related assessments.

Independent Data Monitoring Committee:

An IDMC comprised of independent experts will be convened to review the unblinded safety and tolerability data and the unblinded efficacy data from the interim analyses, in order to recommend to the sponsor whether or not to limit recruitment to any treatment arm.

Following the reviews, the IDMC will recommend whether the study should continue unchanged, be stopped, or be modified in any way.

Full details of the IDMC procedures, processes, and interim analyses can be found in the IDMC Charter.

CCI analyses of efficacy data will be conducted during the study, the CCI when approximately CCI patients have been enrolled (approximately CCI patients in the ceralasertib and durvalumab combination therapy arm and approximately CCI patients in the ceralasertib monotherapy arm) with approximately CCI follow up and the CCI when approximately CCI patients have been enrolled (approximately CCI patients in the ceralasertib and durvalumab combination therapy arm and approximately CCI patients in the ceralasertib monotherapy arm) with approximately CCI weeks follow up.

Statistical Methods

Main study: Each treatment arm is experimental and thus will be analysed separately for objective response rate (ORR). The study will recruit approximately 100 patients in the ceralasertib and durvalumab combination therapy arm. With 100 patients the expected CCI width of the CCI% confidence interval (CI) for ORR will be up to approximately CCI% when the proportion of patients with an objective response is in the rangeCCI% to CCI%. A secondary objective is to compare the ORR between the two treatment arms. With 150 patients (100 patients randomised to the ceralasertib and durvalumab combination therapy arm and 50 patients randomised to the ceralasertib monotherapy arm), there will be at least CCI% power at a CCI of CCI to detect a difference in ORR, assuming an ORR for ceralasertib plus durvalumab of CCI% and an ORR for ceralasertib monotherapy of CCI%.

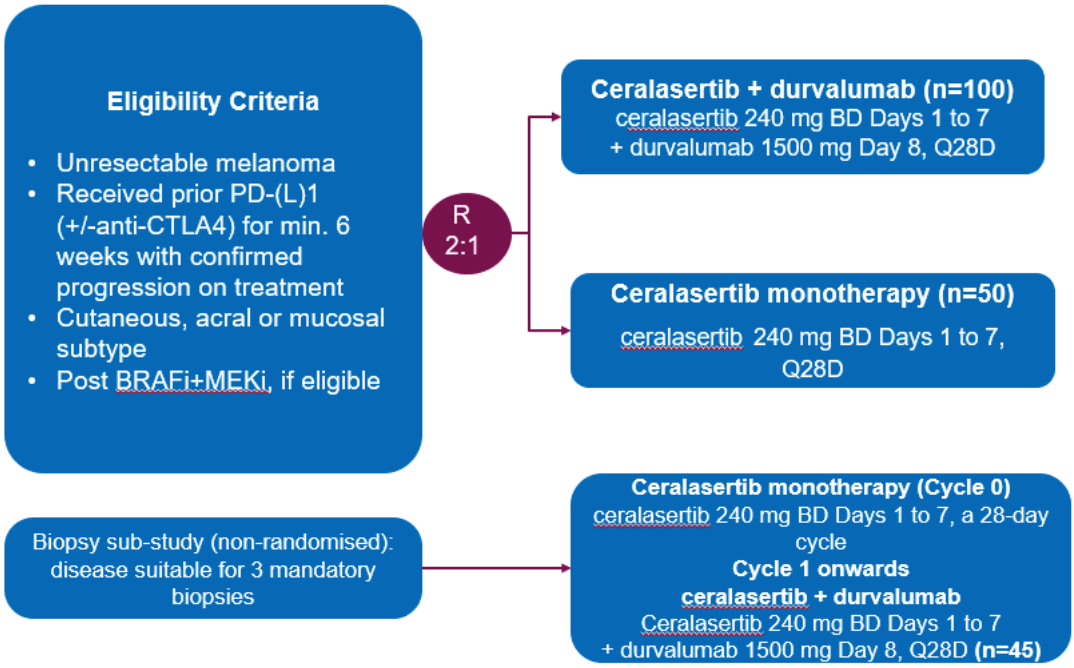
The primary analysis will be conducted once all randomised patients have had a minimum of CCI of follow-up after start of study treatment or have discontinued from the study, whichever occurs first. The primary analysis of ORR will be based on blinded independent central review (BICR) according to RECIST 1.1 using the safety analysis set. As primary analysis, ORR will be summarised for each treatment arm with 95% CI (Clopper-Pearson). As a secondary objective ORR will be compared between the treatment arms using logistic regression adjusting for PD-(L)1 resistance type and lactate dehydrogenase (LDH) per randomisation stratification as covariates. The odds ratio with corresponding 95% CI and p-value will be estimated. This comparative analysis will be provided using the full analysis set. Time to event endpoints of duration of response (DoR), progression free survival (PFS), and overall survival (OS) will be summarised descriptively by Kaplan-Meier method, including the medians, and landmark estimates with corresponding 95% CI. Comparison between the treatment arms will be conducted using a log rank test stratified by PD-(L)1 resistance type and LDH per randomisation stratification. The hazard ratio with corresponding 95% CI will be estimated using a Cox proportional hazards model stratified by PD-(L)1 resistance type and LDH. Time to response (TTR) will be summarised descriptively. The percentage change in target lesion tumour size from baseline at 16 weeks and best percentage change will be summarised visually by waterfall and spider plots. No adjustments for multiplicity are planned.

Safety data will be summarised descriptively and will not be formally analysed unless otherwise specified.

Biopsy sub-study: The sample size of approximately 30 patients with evaluable tumour biopsies at baseline and ceralasertib off-treatment period is designed to give adequate precision in CD8+ T-cells tumour infiltration fold change from baseline. Data will be transformed as appropriate eg, log_2-transformation, and analysed by mixed effect model repeated measures (MMRM) with fixed effect for timepoint and an unstructured variance-covariance matrix to account for repeated measures within a patient. The least squares means for each timepoint will be presented, together with the difference to baseline visit and 95% CI. Association of biomarkers to clinical outcomes will be presented visually, eg, boxplots by Best Overall Response (BOR).

1.2 Schema

Figure 1 Study Design



BD = twice daily; CTLA-4 = cytotoxic T-lymphocyte-associated protein-4; Q28D = every 28 days; BRAFi = BRAF inhibitor; MEKi = MEK inhibitor; min = minimum; PD-(L)1 = programmed death ligand 1; R = randomisation.

1.3 Schedule of Activities

The procedures for this study are presented in the SoA for ceralasertib and durvalumab combination therapy in Table 1, for the ceralasertib monotherapy in Table 2, and for the biopsy sub-study in Table 3.

Table 1 Ceralasertib Plus Durvalumab (Main Study)

Procedure	Screening [a]	Intervention period (28-day cycles)									Post-intervention follow-up period						Details in CSP section or appendix
		Cycles 1-2				Cycle 3			C4-onwards		Study Treatment Discontinued (last dose of study treatment)	Safety follow-up (# of days after last dose)				Progression/Survival Follow-up (Q8W until 18 months, then Q12W)	
Cycle Day	**-21 to -1**	**Day 1**	**Day 7**	**Day 8**	**Day 15**	**Day 1**	**Day 7**	**Day 8**	**Day 1**	**Day 8**		**30 days**	**60 days**	**90 days**	**180 days (6 months)**		
Visit window (± days)	-	-	-	-	**± 1**	**± 3**	-	**± 1**	**± 3**	**± 1**		**± 3**	**± 7**	**± 7**	**± 7**		
Informed consent: main study [b]	X																Section 5 and Appendix A 3
Informed consent: genetic sample and analysis (optional) [b]	X																Section 5.1 and Appendix A 3
Archival tumour sample, mandatory [c]	X																Section 8.6.1
Fresh tumour biopsy [d]	X				X (C2 only)						X (PD)						Section 8.6.1
Inclusion and exclusion criteria [e, f]	X	X															Sections 5.1, 5.2 and 5.4
Demography [g]	X																Section 5.1

Procedure	Screening [a]	Intervention period (28-day cycles)									Post-intervention follow-up period						Details in CSP section or appendix
		Cycles 1-2				Cycle 3			C4-onwards		Study Treatment Discontinued (last dose of study treatment)	Safety follow-up (# of days after last dose)				Progression/Survival Follow-up (Q8W until 18 months, then Q12W)	
Cycle Day	**-21 to -1**	**Day 1**	**Day 7**	**Day 8**	**Day 15**	**Day 1**	**Day 7**	**Day 8**	**Day 1**	**Day 8**		**30 days**	**60 days**	**90 days**	**180 days (6 months)**		
Visit window (± days)	**-**	**-**	**-**	**-**	**± 1**	**± 3**	**-**	**± 1**	**± 3**	**± 1**		**± 3**	**± 7**	**± 7**	**± 7**		
Prior anti-cancer therapy [h]	X																Section 5.1
Full physical examination [a]	X	X				X			X		X	X	X	X	X		Section 8.2.1
Targeted physical examination [i]				X	X			X		X							Section 8.2.1
Height	X																Section 8.2.1
Weight [a]	X	X		X		X		X	X	X	X	X	X	X	X		Section 8.2.1
Past and current medical conditions	X	X [a]															Sections 5.1 and 5.2
12-lead ECG [j, k]	X (Triplicate)	As clinically indicated; single ECGs															Section 8.2.3
Echocardiogram/MUGA	X	As clinically indicated									X						Section 8.2.6.1
Vital signs [k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Section 8.2.2

Procedure	Screening [a]	Intervention period (28-day cycles)									Post-intervention follow-up period						Details in CSP section or appendix
		Cycles 1-2				Cycle 3			C4-onwards		Study Treatment Discontinued (last dose of study treatment)	Safety follow-up (# of days after last dose)				Progression/Survival Follow-up (Q8W until 18 months, then Q12W)	
Cycle Day	-21 to -1	Day 1	Day 7	Day 8	Day 15	Day 1	Day 7	Day 8	Day 1	Day 8		30 days	60 days	90 days	180 days (6 months)		
Visit window (± days)	-	-	-	-	± 1	± 3	-	± 1	± 3	± 1		± 3	± 7	± 7	± 7		
ECOG performance status [l]	X	X		X		X		X	X		X	X	X	X	X	X	Section 8.2.4
Hepatitis B and C and HIV screening	X																Sections 5.1 and 8.2.5
Safety laboratory assessments (clinical chemistry including TSH, haematology, urinalysis [f, k, m])	X	X		X	X	X		X	X	X	X	X	X	X			Section 8.2.5
Coagulation parameters [n]	X	X															Section 8.2.5
Pregnancy test (WOCBP only) [o]	X	X				X			X			X	X	X			Section 8.2.5
AE	X	←========== X ==========→ At every visit and may be conducted by phone if not tied to a visit.															Section 8.3
Concomitant medications	X	←========== X ==========→ At every visit and may be conducted by phone if not tied to a visit.															Section 6.5

Procedure	Screening [a]	Intervention period (28-day cycles)									Post-intervention follow-up period					Details in CSP section or appendix
		Cycles 1-2				Cycle 3			C4-onwards		Study Treatment Discontinued (last dose of study treatment)	Safety follow-up (# of days after last dose)			Progression/Survival Follow-up (Q8W until 18 months, then Q12W)	
Cycle Day	**-21 to -1**	**Day 1**	**Day 7**	**Day 8**	**Day 15**	**Day 1**	**Day 7**	**Day 8**	**Day 1**	**Day 8**		**30 days**	**60 days**	**90 days**	**180 days (6 months)**	
Visit window (± days)	-	-	-	-	± 1	± 3	-	± 1	± 3	± 1		± 3	± 7	± 7	± 7	
Tumour imaging (RECIST 1.1; CT/MRI including brain scan at baseline) [p, s]	X [q]					X	Tumour assessments will be conducted every 8 weeks (±1 week) after start of treatment (C1D1) up to 18 months, then every 12 weeks (±1 week) until objective disease progression per RECIST 1.1. If a patient discontinues without disease progression, RECIST tumour assessments will be performed every 8 weeks for 18 months, then every 12 weeks, thereafter.								Section 8.1.1
CCI																

Procedure	Screening [a]	Intervention period (28-day cycles)									Post-intervention follow-up period						Details in CSP section or appendix
		Cycles 1-2				Cycle 3			C4-onwards		Study Treatment Discontinued (last dose of study treatment)	Safety follow-up (# of days after last dose)				Progression/Survival Follow-up (Q8W until 18 months, then Q12W)	
Cycle Day	-21 to -1	Day 1	Day 7	Day 8	Day 15	Day 1	Day 7	Day 8	Day 1	Day 8		30 days	60 days	90 days	180 days (6 months)		
Visit window (± days)	-	-	-	-	± 1	± 3	-	± 1	± 3	± 1		± 3	± 7	± 7	± 7		
CCI [redacted]																	
Blood sample for ceralasertib PK testing [u]			X				X										Section 8.5.1
Blood sample for durvalumab PK testing [u]				X				X						X			Section 8.5.1
Blood sample for durvalumab immunogenicity testing [v]	X			X				X		X Every 4 cycles	X			X	X		Section 8.5.2
Randomisation [w]		X															Section 6.3
Ceralasertib study treatment (dispensed or returned)		X				X			X		X (returned)						Sections 6.2.2.2 and 6.4

Procedure	Screening [a]	Intervention period (28-day cycles)									Post-intervention follow-up period						Details in CSP section or appendix
		Cycles 1-2				Cycle 3			C4-onwards		Study Treatment Discontinued (last dose of study treatment)	Safety follow-up (# of days after last dose)				Progression/Survival Follow-up (Q8W until 18 months, then Q12W)	
Cycle Day	**-21 to -1**	**Day 1**	**Day 7**	**Day 8**	**Day 15**	**Day 1**	**Day 7**	**Day 8**	**Day 1**	**Day 8**		**30 days**	**60 days**	**90 days**	**180 days (6 months)**		
Visit window (± days)	-	-	-	-	± 1	± 3	-	± 1	± 3	± 1		± 3	± 7	± 7	± 7		
Dosing with ceralasertib (self-administered) [x]		X (Days 1 to 7)				X (Days 1 to 7)			X (Days 1 to 7)								Sections 6.2.2.2 and 6.4
Dosing with durvalumab (IV infusion) [x]				X				X		X							Sections 6.2.1.2 and 6.2.1.3
Dosing diary [y, aa]		X (Days 1 to 7 of every cycle)															Section 6.4
CCI																	

Procedure	Screening [a]	Intervention period (28-day cycles)									Post-intervention follow-up period						Details in CSP section or appendix
		Cycles 1-2				Cycle 3			C4-onwards		Study Treatment Discontinued (last dose of study treatment)	Safety follow-up (# of days after last dose)				Progression/Survival Follow-up (Q8W until 18 months, then Q12W)	
Cycle Day	-21 to -1	Day 1	Day 7	Day 8	Day 15	Day 1	Day 7	Day 8	Day 1	Day 8		30 days	60 days	90 days	180 days (6 months)		
Visit window (± days)	-	-	-	-	± 1	± 3	-	± 1	± 3	± 1		± 3	± 7	± 7	± 7		
CCI																	
PRO training/set up [aa]	X	X															Section 8.1.3.1
Survival status [bb]												X	X	X	X	X	Sections 7.1.3 and 8.1.2
Subsequent anticancer therapy [cc]											X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	Section 7.1.2

[a] If screening assessments have been performed within 3 days prior to starting study intervention, they do not have to be repeated at Cycle 1 Day 1 if the patient's condition has not changed.

[b] Written informed consent and any locally required privacy act document authorisation must be obtained prior to performing any protocol-specific procedures, including screening/baseline evaluations.

[c] Submission of archival tumour tissue is mandatory for all patients. A minimum of 20 freshly cut unstained sections from the archival tumour block are accepted if tumour blocks cannot be submitted, however tumour tissue blocks are preferred.

[d] Fresh tumour biopsies are mandatory, if medically feasible, in all patients with biopsiable disease at screening. However, if patients do not have disease suitable for biopsy, they are required to provide a tumour sample collected within 5 years prior to study entry. Optional on-treatment biopsies will be collected at Cycle 2 between Day 15 and Day 28 and at disease progression, only if a fresh tumour sample was provided at screening. Optional on-treatment biopsies are not required if a fresh tumour sample was not collected at screening. For sample collection details refer to Section 8.6 of the protocol.

[e] Submission of the cytological or histological report, and molecular report confirming BRAF mutation status is mandatory at screening. In addition, the investigator must confirm the type of PD-(L)1 resistance at screening and whether the LDH is normal or above upper limit of normal, in order to stratify the patients accordingly. Other genomic characteristics will be collected where known eg, NRAS, c-kit, PD-(L)1, NF1, MSI.

[f] Clinical laboratory assessment parameters are to be assessed at baseline on Day 1 (unless all screening laboratory assessments are performed within 3 days prior to Day 1) and full blood count result should be checked prior to dosing when assessed on a dosing day. Serum or plasma clinical chemistry (including LFT monitoring) and haematology may be performed more frequently if clinically indicated. Urinalysis should be performed at baseline (screening) and then as clinically indicated. Thyroid stimulating hormone testing is to be done at the timepoints indicated and also when clinically indicated (clinically suspecting immune-related hypo/hyper thyroidism). Free T3 or free T4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.

[g] Baseline demographics will include all prior treatments (start/stop dates, best response, treatment line, reason for treatment discontinuation and, if due to RECIST 1.1-defined disease progression, how progression was determined and dates of radiographic scans indicating disease progression) and disease stage at diagnosis and at study entry. Other genomic characteristics will be collected where known eg, NRAS, c-kit, PD-(L)1, NF1, MSI.

[h] Collect data on prior anti-cancer therapies, including best response, setting (eg, adjuvant/metastatic), prior radiotherapy, and prior surgery. For the prior anti-PD-(L)1 regimen, also collect reason for discontinuation and details of scans indicating RECIST 1.1-defined disease progression, including anonymised copies of the scan reports.

[i] Additional physical examination will be performed, if clinically indicated.

[j] Triplicate ECGs at screening only. Subsequent ECGs should only be taken if clinically indicated.

[k] Whenever ECG, vital signs and blood draws are scheduled on the same day, it is recommended that the assessments occur in the following order: vital signs, ECG, and then blood draws. The timing of the ECG and vital signs assessments must allow for the blood draw (eg, PK blood sample) to occur at the scheduled time points.

[l] ECOG assessment also to be performed at initiation of subsequent anticancer therapy, where possible. In addition, ECOG performance status should be collected at initiation of subsequent anticancer therapy, if appropriate site staff are available to collect such information. Additional ECOG assessments may be performed (eg, on Day 15), if clinically indicated.

[m] Patients who develop a ≥ Grade 3 of anaemia, neutropenia, or thrombocytopenia during the treatment period will also need to have additional assessments on Day 15 (for combination of ceralasertib and durvalumab) until there is no evidence of ≥ Grade 3 anaemia, neutropenia, or thrombocytopenia for at least 2 cycles.

[n] Coagulation will be performed at screening and as clinically indicated during subsequent visits.

[o] Women of childbearing potential only. Serum pregnancy test at screening, urine test at other time points up to 90 days after the last dose of study treatment. For country-specific requirements for Belgium and France see Appendices K 1.1 and K 1.2, respectively.

[p] CT scans of the chest, abdomen, and pelvis (or MRI where CT is contraindicated) should be conducted every 8 weeks (±1 week) after the start of study treatment (Cycle 1 Day 1) up to 18 months, then every 12 weeks (±1 week) until objective disease progression as per RECIST 1.1, irrespective of treatment decisions. In the event of study treatment interruptions or delays, tumour assessments should proceed to schedule relative to Cycle 1 Day 1. Soft tissue or visceral progression observed by CT or MRI, according to RECIST 1.1, does not require a confirmatory scan. To confirm progression based on non-target lesions, additional scans or images/photographs may be required for submission for BICR.

[q] Baseline contrast enhanced MRI brain scan assessment (or CT if MRI is contraindicated) for all patients at screening.

[r] CCI

[s] CCI

[t] CCI

[u] For ceralasertib, PK sample will be collected in all patients at pre-dose (up to 1 hour prior) and 1 hour (± 30 min) post-dose on Day 7 of each cycle, for the first 3 cycles. For durvalumab, PK sample will be collected in all patients at pre-dose (up to 1 hour prior) and 1 hour (± 30 min) post-dose on Day 8 of each cycle, for the first 3 cycles. For non-dosing days, PK sample will be collected at similar times as dosing day.

[v] Immunogenicity sample for durvalumab to be collected at screening, then pre-dose on Day 8 of Cycles 1, 2, 3, and 4, then every 4 cycles, end of treatment, 90 days and 6 months (± 7 days) after last dose.

[w] Every effort should be made to minimise the time between randomisation and starting treatment (ie, within 3 business days of randomisation).

[x] Ceralasertib administered twice daily from Days 1 to 7 of each cycle. Durvalumab administered on Day 8 of each cycle.

[y] For ceralasertib, patients will be required to complete a dosing diary (e-diary) from Day 1 to Day 7 of each cycle, using an electronic device. The dosing diary must be reviewed by the designated study personnel on Day 1 of each cycle.

[z] CCI

[aa] The device/e-diary should be fully charged, and checked that it is fully functioning, prior to the patient's first dosing visit. The site should ensure the patient is trained and understands how to use the PRO device/doing diary prior to the first use.

[bb] Survival status collected 8 weekly reducing to 12 weekly after 18 months.

[cc] Other anti-cancer therapies collected 8 weekly reducing to 12 weekly after 18 months. Off study treatment follow-up: subsequent anti-cancer therapies to be collected.

AE = adverse events; ATM = ataxia telangiectasia mutated; BICR = Blinded independent central review; BRAF = B-Rapidly Accelerated Fibrosarcoma gene; C = cycle; CR = complete response; CSP = clinical study protocol; CT = computed tomography; CCI ; d = day; CCI ; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; CCI CCI ; IL = Item Library; IV = intravenous; MRI = magnetic resonance imaging; MSI = microsatellite instability; MUGA = multigated acquisition; NF1 = neurofibromatosis type 1; CCI ; PD-(L)1 = programmed death ligand 1; CCI ; PK = pharmacokinetic; PRO = patient-reported outcomes; CCI ; RECIST = Response Evaluation Criteria in Solid Tumours; CCI ; SAE = serious adverse event; SD = stable disease; SoC = standard of care; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone; WOCBP = women of childbearing potential.

Table 2 Ceralasertib Monotherapy (Main Study)

Procedure	Screening [a]	Intervention period (28-day cycles)								Post-intervention follow-up period			Details in CSP section or appendix
		Cycles 1-2			Cycle 3			C4-onwards		Study Treatment Discontinued (Last dose of study treatment)	Safety follow-up	Progression/Survival Follow-up	
Cycle Day	**-21 to -1**	**Day 1**	**Day 7**	**Day 15**	**Day 1**	**Day 7**	**Day 15**	**Day 1**	**Day 15**		**30 days after last dose**	**(Q8W until 18 months, then Q12W)**	
Visit window (± days)	-	-	-	± 1	± 3	-	± 1	± 3	± 1		± 3	± 7	
Informed consent: main study [b]	X												Section 5 and Appendix A 3
Informed consent: genetic sample and analysis (optional) [b]	X												Section 5.1 and Appendix A 3
Archival tumour sample, mandatory [c]	X												Section 8.6.1
Fresh tumour biopsy [d]	X			X (C2 only)						X (PD)			Section 8.6.1
Inclusion and exclusion criteria [e, f]	X	X											Sections 5.1, 5.2 and 5.4
Demography [g]	X												Section 5.1
Prior anti-cancer therapy [h]	X												Section 5.1
Full physical examination [a]	X	X			X			X		X	X		Section 8.2.1
Targeted physical examination [i]			X	X		X	X		X				Section 8.2.1

Procedure	Screening [a]	Intervention period (28-day cycles)								Post-intervention follow-up period			Details in CSP section or appendix
		Cycles 1-2			Cycle 3			C4-onwards		Study Treatment Discontinued (Last dose of study treatment)	Safety follow-up	Progression/Survival Follow-up	
Cycle Day	**-21 to -1**	**Day 1**	**Day 7**	**Day 15**	**Day 1**	**Day 7**	**Day 15**	**Day 1**	**Day 15**		**30 days after last dose**	**(Q8W until 18 months, then Q12W)**	
Visit window (± days)	-	-	-	± 1	± 3	-	± 1	± 3	± 1		± 3	± 7	
Height	X												Section 8.2.1
Weight [a]	X	X		X	X		X	X	X	X	X		Section 8.2.1
Past and current medical conditions	X	X [a]											Sections 5.1 and 5.2
12-lead ECG [j, k]	X (Triplicate)	As clinically indicated; single ECGs											Section 8.2.3
Echocardiogram/MUGA	X	As clinically indicated								X			Section 8.2.6.1
Vital signs [k]	X	X	X	X	X	X	X	X	X	X	X		Section 8.2.2
ECOG performance status [l]	X	X			X			X		X			Section 8.2.4
Hepatitis B and C and HIV screening	X												Section 5.1 and 8.2.5
Safety laboratory assessments (clinical chemistry including TSH, haematology, urinalysis) [f, k, m]	X	X	X	X	X	X	X	X	X	X	X		Section 8.2.5

Procedure	Screening [a]	Intervention period (28-day cycles)								Post-intervention follow-up period			Details in CSP section or appendix
		Cycles 1-2			Cycle 3			C4-onwards		Study Treatment Discontinued (Last dose of study treatment)	Safety follow-up	Progression/Survival Follow-up	
Cycle Day	-21 to -1	Day 1	Day 7	Day 15	Day 1	Day 7	Day 15	Day 1	Day 15		30 days after last dose	(Q8W until 18 months, then Q12W)	
Visit window (± days)	-	-	-	± 1	± 3	-	± 1	± 3	± 1		± 3	± 7	
Coagulation parameters [n]	X	X											Section 8.2.5
Pregnancy test (WOCBP only) [o]	X	X			X			X			X		Section 8.2.5
AE	X	←========== X ========== → At every visit and may be conducted by phone if not tied to a visit.											Section 8.3
Concomitant medications	X	←========== X ========== → At every visit and may be conducted by phone if not tied to a visit.											Section 6.5
Tumour imaging (RECIST 1.1; CT/MRI including brain scan at baseline) [p, s]	X [q]				X	Tumour assessments will be conducted every 8 weeks (±1 week) after start of treatment (C1D1) up to 18 months, then every 12 weeks (±1 week) until objective disease progression per RECIST 1.1. If a patient discontinues without disease progression, RECIST tumour assessments will be performed every 8 weeks for 18 months, then every 12 weeks, thereafter.						Section 8.1.1
CCI [redacted]													

Procedure	Screening [a]	Intervention period (28-day cycles)								Post-intervention follow-up period			Details in CSP section or appendix
		Cycles 1-2			Cycle 3			C4-onwards		Study Treatment Discontinued (Last dose of study treatment)	Safety follow-up	Progression/Survival Follow-up	
Cycle Day	-21 to -1	Day 1	Day 7	Day 15	Day 1	Day 7	Day 15	Day 1	Day 15		30 days after last dose	(Q8W until 18 months, then Q12W)	
Visit window (± days)	-	-	-	± 1	± 3	-	± 1	± 3	± 1		± 3	± 7	
CCI													
Blood sample for ceralasertib PK testing [u]			X			X							Section 8.5.1
Randomisation [v]		X											Section 6.3

Procedure	Screening [a]	Intervention period (28-day cycles)								Post-intervention follow-up period			Details in CSP section or appendix
		Cycles 1-2			Cycle 3			C4-onwards		Study Treatment Discontinued (Last dose of study treatment)	Safety follow-up	Progression/Survival Follow-up	
Cycle Day	**-21 to -1**	**Day 1**	**Day 7**	**Day 15**	**Day 1**	**Day 7**	**Day 15**	**Day 1**	**Day 15**		**30 days after last dose**	**(Q8W until 18 months, then Q12W)**	
Visit window (± days)	**-**	**-**	**-**	**± 1**	**± 3**	**-**	**± 1**	**± 3**	**± 1**		**± 3**	**± 7**	
Ceralasertib study treatment (dispensed or returned)		X			X			X		X (returned)			Sections 6.2.2.2 and 6.4
Dosing with ceralasertib (self-administered) [w]		X (Days 1 to 7 of every cycle)			X (Days 1 to 7 of every cycle)			X (Days 1 to 7 of every cycle)					Sections 6.2.2.2 and 6.4
Dosing diary [x, z]		X (Days 1 to 7 of every cycle)											Section 6.4
CCI													

Procedure	Screening [a]	Intervention period (28-day cycles)								Post-intervention follow-up period			Details in CSP section or appendix
		Cycles 1-2			Cycle 3			C4-onwards		Study Treatment Discontinued (Last dose of study treatment)	Safety follow-up	Progression/Survival Follow-up	
Cycle Day	-21 to -1	Day 1	Day 7	Day 15	Day 1	Day 7	Day 15	Day 1	Day 15		30 days after last dose	(Q8W until 18 months, then Q12W)	
Visit window (± days)	-	-	-	± 1	± 3	-	± 1	± 3	± 1		± 3	± 7	
CCI													
PRO training/set up [z]	X	X											Section 8.1.3.1
Survival status [aa]											X	X	Sections 7.1.3 and 8.1.2
Subsequent anticancer therapy [bb]										X	X	X	Section 7.1.2

[a] If screening assessments have been performed within 3 days prior to starting study intervention, they do not have to be repeated at Cycle 1 Day 1 if the patient's condition has not changed.

[b] Written informed consent and any locally required privacy act document authorisation must be obtained prior to performing any protocol-specific procedures, including screening/baseline evaluations.

[c] Submission of archival tumour tissue is mandatory for all patients. A minimum of 20 freshly cut unstained sections from the archival tumour block are accepted if tumour blocks cannot be submitted, however tumour tissue blocks are preferred.

[d] Fresh tumour biopsies are mandatory in all patients with biopsiable disease at screening. However, if patients do not have disease suitable for biopsy, they are required to provide a tumour sample collected within 5 years prior to study entry. Optional on-treatment biopsies will be collected at Cycle 2 between Day 15 and Day 28 for ceralasertib monotherapy and at disease progression, only if a fresh tumour sample was provided at screening. Optional on-treatment biopsies are not required if a fresh tumour sample was not collected at screening. For sample collection details refer to Section 8.6 of the protocol.

[e] Submission of the cytological or histological report, and molecular report confirming BRAF mutation status is mandatory at screening. In addition, the investigator must confirm the type of PD-(L)1 resistance at screening and whether the LDH is normal or above upper limit of normal, in order to stratify the patients accordingly. Other genomic characteristics will be collected where known eg, NRAS, c-kit, PD-(L)1, NF1, MSI.

[f] Clinical laboratory assessment parameters are to be assessed at baseline on Day 1 (unless all screening laboratory assessments are performed within 3 days prior to Day 1) and full blood count result should be checked prior to dosing when assessed on a dosing day. Serum or plasma clinical chemistry (including LFT monitoring) and haematology may be performed more frequently if clinically indicated. Urinalysis should be performed at baseline (screening) and then as clinically indicated. Thyroid stimulating hormone testing is to be done at the timepoints indicated and also when clinically indicated (clinically suspecting immune-related hypo/hyper thyroidism). Free T3 or free T4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.

[g] Baseline demographics will include all prior treatments (start/stop dates, best response, treatment line, reason for treatment discontinuation and, if due to RECIST 1.1-defined disease progression, how progression was determined and dates of radiographic scans indicating disease progression per RECIST 1.1) and disease stage at diagnosis and at study entry. Other genomic characteristics will be collected where known eg, NRAS, c-kit, PD-(L)1, NF1, MSI.

[h] Collect prior anti-cancer therapies, including best response, setting (eg, adjuvant/metastatic), prior radiotherapy, and prior surgery. For the prior anti-PD-(L)1 regimen, also collect reason for discontinuation and details of scans indicating RECIST 1.1 disease progression, including anonymised copies of the scan reports.

[i] Additional physical examination will be performed, if clinically indicated.

[j] Triplicate ECGs at screening only. Subsequent ECGs should only be taken if clinically indicated.

[k] Whenever ECG, vital signs and blood draws are scheduled on the same day, it is recommended that the assessments occur in the following order: vital signs, ECG, and then blood draws. The timing of the ECG and vital signs assessments must allow for the blood draw (eg, PK blood sample) to occur at the scheduled time points.

[l] ECOG assessment also to be performed at initiation of subsequent anticancer therapy, where possible. In addition, ECOG performance status should be collected at initiation of subsequent anticancer therapy, if appropriate site staff are available to collect such information. Additional ECOG assessments may be performed (eg, on Day 15), if clinically indicated.

[m] Patients who develop a ≥ Grade 3 of anaemia, neutropenia, or thrombocytopenia during the treatment period will also need to have additional assessments on Day 7 (for ceralasertib monotherapy) until there is no evidence of ≥ Grade 3 anaemia, neutropenia, or thrombocytopenia for at least 2 cycles.

[n] Coagulation will be performed at screening and as clinically indicated during subsequent visits. For country-specific requirements for Belgium see Appendix K 1.1.

[o] Women of childbearing potential only. Serum pregnancy test at screening, urine test at other time points up to 30 days after the last dose of study treatment. For country-specific requirements for Belgium and France see Appendices K 1.1 and K 1.2, respectively.

[p] Computed tomography scans of the chest, abdomen, and pelvis (or MRI where CT is contraindicated) should be conducted every 8 weeks (±1 week) after the start of treatment (Cycle 1 Day 1) up to 18 months, then every 12 weeks (±1 week) until objective disease progression as per RECIST 1.1, irrespective of treatment decisions. In the event of treatment interruptions or delays, tumour assessments should proceed to schedule relative to Cycle 1 Day 1. Soft tissue or visceral progression observed by CT or MRI, according to RECIST 1.1, does not require a confirmatory scan. To confirm progression based on non-target lesions, additional scans or images/photographs may be required for submission for BICR.

[q] Baseline contrast enhanced MRI brain scan assessment (or CT if MRI is contraindicated) for all patients at screening.

[r] CCI

[s] CCI

[t] CCI

[u] PK samples will be collected in all patients at pre-dose (up to 1 hour prior) and 1 hour (± 30 min) post-dose on D7 of each cycle, for the first 3 cycles.

[v] Every effort should be made to minimise the time between randomisation and starting treatment (ie, within 3 business days of randomisation).

[w] Ceralasertib administered twice daily from Days 1 to 7 of each cycle.

[x] For ceralasertib, patients will be required to complete a dosing diary (e-diary) from Day 1 to Day 7 of each cycle, using an electronic device. The dosing diary must be reviewed by the designation study personnel on Day 1 of each cycle.

[y] CCI [redacted]

[z] The device/e-diary should be fully charged, and checked that it is fully functioning, prior to the patient's first dosing visit. The site should ensure the patient is trained and understands how to use the PRO device/dosing diary prior to the first use.

[aa] Survival status collected 8 weekly, reducing to 12 weekly after 18 months.

[bb] Other anti-cancer therapies collected 8 weekly, reducing to 12 weekly after 18 months. Off study treatment follow-up: subsequent anti-cancer therapies to be collected.

AE = adverse events; ATM = ataxia telangiectasia mutated; BICR = Blinded independent central review; BRAF = B-Rapidly Accelerated Fibrosarcoma gene; C = cycle; CR = complete response; CSP = clinical study protocol; CT = computed tomography; CCI [redacted]; d = day; CCI [redacted]; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; CCI [redacted]; HIV = human immunodeficiency virus; CCI [redacted]; MRI = magnetic resonance imaging; MSI = microsatellite instability; MUGA = multigated acquisition; NF1 = neurofibromatosis type 1; CCI [redacted]; PD-(L)1 = programmed death ligand 1; CCI [redacted]; PK = pharmacokinetic; CCI [redacted]; RECIST = Response Evaluation Criteria in Solid Tumours; CCI [redacted]; SAE = serious adverse event; SD = stable disease; SoC = standard of care; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone; WOCBP = women of childbearing potential.

Table 3 Biopsy Sub-study

Procedure	Screening [a]	Intervention period (28-day cycles)										Post-intervention follow-up period						Details in CSP section or appendix
		Cycle 0				Cycle 1				C2-onwards		Study Treatment Discontinued (last dose of study treatment)	Safety follow-up (# of days after last dose)				Progression/Survival Follow-up (Q8W until 18 months, then Q12W)	
Cycle Day	-21 to -1	Day 1	Day 7	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8		30 days	60 days	90 days	180 days (6 months)		
Visit window (± days)	-	-	-	-	± 1	± 3	-	± 1		± 3	± 1		± 3	± 7	± 7	± 7		
Informed consent: main study [b]	X																	Section 5 and Appendix A 3
Informed consent: genetic sample and analysis (optional) [b]	X																	Section 5.1 and Appendix A 3
Archival tumour sample, mandatory [c]	X																	Section 8.6.1
Fresh tumour biopsy [d]	X		X	X (between D15 and D28)								X (PD; optional)						Section 8.6.1
Inclusion and exclusion criteria [e, f]	X	X																Sections 5.1, 5.2 and 5.4
Demography [g]	X																	Section 5.1

Procedure	Screening [a]	Intervention period (28-day cycles)										Post-intervention follow-up period						Details in CSP section or appendix
		Cycle 0				Cycle 1				C2-onwards		Study Treatment Discontinued (last dose of study treatment)	Safety follow-up (# of days after last dose)				Progression/Survival Follow-up (Q8W until 18 months, then Q12W)	
Cycle Day	-21 to -1	Day 1	Day 7	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8		30 days	60 days	90 days	180 days (6 months)		
Visit window (± days)	-	-	-	-	± 1	± 3	-	± 1		± 3	± 1		± 3	± 7	± 7	± 7		
Prior anti-cancer therapy [h]	X																	Section 5.1
Full physical examination [a]	X	X				X				X		X	X	X	X	X		Section 8.2.1
Targeted physical examination [i]			X	X	X		X	X	X		X							Section 8.2.1
Height	X																	Section 8.2.1
Weight [a]	X	X		X		X	X			X	X	X	X	X	X	X		Section 8.2.1
Past and current medical conditions	X	X [a]																Sections 5.1 and 5.2
12-lead ECG [j, k]	X (Triplicate)	As clinically indicated; single ECGs																Section 8.2.3
Echocardiogram/MUGA	X	As clinically indicated										X						Section 8.2.6.1

Procedure	Screening [a]	Intervention period (28-day cycles)										Post-intervention follow-up period						Details in CSP section or appendix
		Cycle 0				Cycle 1				C2-onwards		Study Treatment Discontinued (last dose of study treatment)	Safety follow-up (# of days after last dose)				Progression/Survival Follow-up (Q8W until 18 months, then Q12W)	
Cycle Day	**-21 to -1**	**Day 1**	**Day 7**	**Day 15**	**Day 22**	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 1**	**Day 8**		**30 days**	**60 days**	**90 days**	**180 days (6 months)**		
Visit window (± days)	**-**	**-**	**-**	**-**	**± 1**	**± 3**	**-**	**± 1**		**± 3**	**± 1**		**± 3**	**± 7**	**± 7**	**± 7**		
Vital signs [k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Section 8.2.2
ECOG performance status [l]	X	X				X				X		X	X	X	X	X	X	Section 8.2.4
Hepatitis B and C and HIV screening	X																	Sections 5.1 and 8.2.5
Safety laboratory assessments (clinical chemistry including TSH, haematology, urinalysis) [f, k, m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Section 8.2.5
Coagulation parameters [n]	X	X																Section 8.2.5
Pregnancy test (WOCBP only) [o]	X	X				X				X			X	X	X			Section 8.2.5
AE	X	←========== X ========== → At every visit and may be conducted by phone if not tied to a visit.																Section 8.3

Procedure	Screening [a]	Intervention period (28-day cycles)										Post-intervention follow-up period					Details in CSP section or appendix
		Cycle 0				Cycle 1				C2-onwards		Study Treatment Discontinued (last dose of study treatment)	Safety follow-up (# of days after last dose)			Progression/Survival Follow-up (Q8W until 18 months, then Q12W)	
Cycle Day	**-21 to -1**	**Day 1**	**Day 7**	**Day 15**	**Day 22**	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 1**	**Day 8**		**30 days**	**60 days**	**90 days**	**180 days (6 months)**	
Visit window (± days)	-	-	-	-	± 1	± 3	-	± 1		± 3	± 1		± 3	± 7	± 7	± 7	
Concomitant medications	X	←========== X ==========→ At every visit and may be conducted by phone if not tied to a visit.															Section 6.5
Tumour imaging (RECIST 1.1; CT/MRI including brain scan at baseline) [p]	X [q]					X		Tumour assessments will be conducted every 8 weeks (±1 week) after start of treatment (C1D1) up to 18 months, then every 12 weeks (±1 week) until objective disease progression per RECIST 1.1. If a patient discontinues without disease progression, RECIST tumour assessments will be performed 8 weekly for 18 months, then 12 weekly, thereafter.								Section 8.1.1

CCI

[redacted]

Procedure	Screening [a]	Intervention period (28-day cycles)										Post-intervention follow-up period					Details in CSP section or appendix
		Cycle 0				Cycle 1				C2-onwards		Study Treatment Discontinued (last dose of study treatment)	Safety follow-up (# of days after last dose)			Progression/Survival Follow-up (Q8W until 18 months, then Q12W)	
Cycle Day	-21 to -1	Day 1	Day 7	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8		30 days	60 days	90 days	180 days (6 months)	
Visit window (± days)	-	-	-	-	± 1	± 3	-	± 1		± 3	± 1		± 3	± 7	± 7	± 7	
CCI																	

Procedure	Screening [a]	Intervention period (28-day cycles)										Post-intervention follow-up period						Details in CSP section or appendix
		Cycle 0				Cycle 1				C2-onwards		Study Treatment Discontinued (last dose of study treatment)	Safety follow-up (# of days after last dose)				Progression/Survival Follow-up (Q8W until 18 months, then Q12W)	
Cycle Day	**-21 to -1**	**Day 1**	**Day 7**	**Day 15**	**Day 22**	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 1**	**Day 8**		**30 days**	**60 days**	**90 days**	**180 days (6 months)**		
Visit window (± days)	-	-	-	-	± 1	± 3	-	± 1		± 3	± 1		± 3	± 7	± 7	± 7		
Blood sample for ceralasertib PK testing [u]		X	X									X (optional if biopsy is collected)						Section 8.5.1
Blood sample for durvalumab PK testing [u]												X			X			Section 8.5.1
Blood sample for durvalumab immunogenicity testing [v]	X											X			X	X		Section 8.5.2
Ceralasertib study treatment (dispensed or returned)		X				X				X		X (returned)						Sections 6.2.2.2 and 6.4

Procedure	Screening [a]	Intervention period (28-day cycles)										Post-intervention follow-up period						Details in CSP section or appendix
		Cycle 0				Cycle 1				C2-onwards		Study Treatment Discontinued (last dose of study treatment)	Safety follow-up (# of days after last dose)				Progression/Survival Follow-up (Q8W until 18 months, then Q12W)	
Cycle Day	-21 to -1	Day 1	Day 7	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8		30 days	60 days	90 days	180 days (6 months)		
Visit window (± days)	-	-	-	-	± 1	± 3	-	± 1		± 3	± 1		± 3	± 7	± 7	± 7		
Dosing with ceralasertib (self-administered) [w]		X [x] (Days 1 to 7)				X (Days 1 to 7 of every cycle)				X (Days 1 to 7 of every cycle)								Sections 6.2.2.2 and 6.4
Dosing with durvalumab (IV infusion) [w]							X				X							Sections 6.2.1.2 and 6.2.1.3
Dosing diary [y, z]		X (Days 1 to 7 of every cycle)																Section 6.4
Survival status [aa]													X	X	X	X	X	Sections 7.1.3 and 8.1.2
Subsequent anticancer therapy [bb]												X	X	X	X	X	X	Section 7.1.2

[a] If screening assessments have been performed within 3 days prior to starting study intervention, they do not have to be repeated at Cycle 1 Day 1 if the patient's condition has not changed.

[b] Written informed consent and any locally required privacy act document authorisation must be obtained prior to performing any protocol-specific procedures, including screening/baseline evaluations.

[c] Submission of archival tumour tissue is mandatory for all patients. A minimum of 20 freshly cut unstained sections from the archival tumour block are accepted if tumour blocks cannot be submitted, however tumour tissue blocks are preferred.

[d] All study patients in the biopsy substudy are required to provide 3 mandatory fresh tumour biopsy samples for testing at Screening (Days -21 to -1), on-ceralasertib treatment, Cycle 0 (on Day 7) of ceralasertib monotherapy, and off-ceralasertib treatment, Cycle 0 (between Days 15 to 28). For sample collection details refer to Section 8.6 of the protocol.

[e] Submission of the cytological or histological report, and molecular report confirming BRAF mutation status is mandatory at screening. In addition, the investigator must confirm the type of PD-(L)1 resistance at screening and whether the LDH is normal or above upper limit of normal, in order to stratify the patients accordingly. Other genomic characteristics will be collected where known eg, NRAS, c-kit, PD-(L)1, NF1, MSI.

[f] Clinical laboratory assessment parameters are to be assessed at baseline on Day 1 (unless all screening laboratory assessments are performed within 3 days prior to Day 1) and full blood count result should be checked prior to dosing when assessed on a dosing day. Serum or plasma clinical chemistry (including LFT monitoring) and haematology may be performed more frequently if clinically indicated. Urinalysis should be performed at baseline (screening) and then as clinically indicated. Thyroid stimulating hormone testing is to be done at the timepoints indicated and also when clinically indicated (clinically suspecting immune-related hypo/hyper thyroidism). Free T3 or free T4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.

[g] Baseline demographics will include all prior treatments (start/stop dates, best response, treatment line, reason for treatment discontinuation and, if due to RECIST 1.1-defined disease progression, how progression was determined and dates of radiographic scans indicating disease progression) and disease stage at diagnosis and at study entry. Other genomic characteristics will be collected where known eg, NRAS, c-kit, PD-(L)1, NF1, MSI.

[h] Collect data on prior anti-cancer therapies, including best response, setting (eg, adjuvant/metastatic), prior radiotherapy, and prior surgery. For the prior anti-PD-(L)1 regimen, also collect reason for discontinuation and details of scans indicating RECIST 1.1-defined disease progression, including anonymised copies of the scan reports.

[i] Additional physical examination will be performed, if clinically indicated.

[j] Triplicate ECGs at screening only. Subsequent ECGs should only be taken if clinically indicated.

[k] Whenever ECG, vital signs and blood draws are scheduled on the same day, it is recommended that the assessments occur in the following order: vital signs, ECG, and then blood draws. The timing of the ECG and vital signs assessments must allow for the blood draw (eg, PK blood sample) to occur at the scheduled time points.

[l] ECOG assessment also to be performed at initiation of subsequent anticancer therapy, where possible. In addition, ECOG performance status should be collected at initiation of subsequent anticancer therapy, if appropriate site staff are available to collect such information. Additional ECOG assessments may be performed (eg, on Day 15), if clinically indicated.

[m] Patients who develop a ≥ Grade 3 of anaemia, neutropenia, or thrombocytopenia during the treatment period will also need to have additional assessments also on Day 15 until there is no evidence of ≥ Grade 3 anaemia, neutropenia, or thrombocytopenia for at least 2 cycles.

[n] Coagulation will be performed at screening and as clinically indicated during subsequent visits.

[o] Women of childbearing potential only. Serum pregnancy test at screening, urine test at other time points up to 90 days after the last dose of study treatment. For country-specific requirements for Belgium and France see Appendices K 1.1 and K 1.2, respectively.

[p] CT scans of the chest, abdomen, and pelvis (or MRI where CT is contraindicated) should be conducted every 8 weeks (±1 week) after the start of study treatment (Cycle 1 Day 1) up to 18 months, then every 12 weeks (±1 week) until objective disease progression as per RECIST 1.1, irrespective of treatment decisions. In the event of study treatment interruptions or delays, tumour assessments should proceed to schedule relative to Cycle 1 Day 1. Soft tissue or visceral progression observed by CT or MRI, according to RECIST 1.1, does not require a confirmatory scan. To confirm progression based on non-target lesions, additional scans or images / photographs may be required for submission for BICR.

[q] Baseline contrast enhanced MRI brain scan assessment (or CT if MRI is contraindicated) for all patients at screening.

[r] CCI

[s] CCI

[t] CCI

[u] For ceralasertib, PK sample will be collected in all patients at pre-dose (up to 1 hour prior) and 1 hour (± 30 min) post-dose on Day 1 and Day 7 of Cycle 0. For durvalumab, PK sample will be collected in all patients at study treatment discontinuation and at 90 days after last dose of the study treatment. For non-dosing days, PK sample will be collected at similar times as dosing day.

[v] Immunogenicity sample for durvalumab to be collected at screening, end of treatment, 90 days and 6 months (± 7 days) after last dose.

[w] Ceralasertib administered twice daily from Days 1 to 7 at Cycle 0 (a 28-day cycle) and at each cycle, Cycle 1 onwards. Durvalumab administered on Day 8 of each cycle, from Cycle 1 onwards.

[x] Cycle 1 may start after the off-treatment biopsy is collected ie, between Cycle 0, Days 15 to 28, and if blood parameters are within limits. For country-specific requirements for Belgium see Appendix K 1.1.

[y] For ceralasertib, patients will be required to complete a dosing diary (e-diary) from Day 1 to Day 7 of each cycle, using an electronic device. The dosing diary must be reviewed by the designated study personnel at Day 1 of each cycle.

[z] The device/e-diary should be fully charged, and checked that it is fully functioning, prior to the patient's first dosing visit. The site should ensure the patient is trained and understands how to use the dosing diary prior to the first use.

[aa] Survival status collected 8 weekly reducing to 12 weekly after 18 months.

[bb] Other anti-cancer therapies collected 8 weekly reducing to 12 weekly after 18 months. Off study treatment follow-up: subsequent anti-cancer therapies to be collected.

AE = adverse events; ATM = ataxia telangiectasia mutated; BICR = Blinded independent central review; BRAF = B-Rapidly Accelerated Fibrosarcoma gene; C = cycle; CR = complete response; CSP = clinical study protocol; CT = computed tomography; CCI ; d = day; CCI ; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; HIV = human immunodeficiency virus; MRI = magnetic resonance imaging; MSI = microsatellite instability; MUGA = multigated acquisition; NF1 = neurofibromatosis type 1; CCI ; PD-(L)1 = programmed death ligand 1; CCI ; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumours; CCI ; SAE = serious adverse event; SD = stable disease; SoC = standard of care; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone; WOCBP = women of childbearing potential.

2 INTRODUCTION

2.1 Study Rationale

This Phase 2 study aims to evaluate the efficacy and safety/tolerability of ceralasertib (AZD6738), when administered as monotherapy and in combination with durvalumab in patients with unresectable or advanced melanoma and primary or secondary resistance to PD-(L)1 inhibition. The rationale for conducting the main study is supported by clinical data from ongoing studies, unmet need, and the evidence of ceralasertib modulating the immune environment.

An open-label, non-randomised, biopsy sub-study is also planned in patients suitable for 3 mandatory biopsies. The rationale for conducting the biopsy sub-study is to understand the MoA of ceralasertib plus durvalumab and investigate ceralasertib as an immune modulator.

The background to the study rationale is summarised in Section 2.2 and Section 2.3. The rationale for study design summarised in Section 4.2 and justification for study treatment dose summarised in Section 4.3.

2.2 Background

2.2.1 Immunotherapies

It is increasingly understood that cancers are recognised by the immune system, and under some circumstances, the immune system may control or even eliminate tumours (Dunn et al 2004).

PD-L1 is part of a complex system of receptors and ligands that are involved in controlling T-cell activation. The PD-1 receptor (cluster of differentiation [CD]279) is expressed on the surface of activated T-cells (Keir et al 2008). It has 2 known ligands: PD-L1 (B7-H1; CD274) and programmed death-ligand 2 (PD-L2) (B7-DC; CD273) (Okazaki and Honjo 2007). PD-1 and PD-L1/PD-L2 belong to a family of immune checkpoint proteins that act as co-inhibitory factors, which can halt or limit the development of T-cell response. When PD-L1 binds to PD-1, an inhibitory signal is transmitted into the T-cell, which reduces cytokine production and suppresses T-cell proliferation. Tumour cells exploit this immune checkpoint pathway as a mechanism to evade detection and inhibit immune response.

PD-L1 is constitutively expressed by B-cells, dendritic cells, and macrophages (Qin et al 2016). Importantly, PD-L1 is commonly over-expressed on tumour cells or on non-transformed cells in the tumour microenvironment (Pardoll 2012). PD-L1 expressed on the tumour cells binds to PD-1 receptors on the activated T-cells, leading to the inhibition of cytotoxic T-cells. These deactivated T-cells remain inhibited in the tumour microenvironment.

The PD-1/PD-L1 pathway represents an adaptive immune resistance mechanism that is exerted by tumour cells in response to endogenous antitumour activity.

The inhibitory mechanism described above is co-opted by tumours that express PD-L1 as a way of evading immune detection and elimination. The binding of an anti-PD-L1 agent to the PD-L1 receptor inhibits the interaction of PD-L1 with the PD-1 and CD80 receptors expressed on immune cells. This activity overcomes PD-L1-mediated inhibition of antitumour immunity. While functional blockade of PD-L1 results in T-cell reactivation, this mechanism of action is different from direct agonism of a stimulatory receptor such as CD28.

PD-L1 is expressed in a broad range of cancers. Based on these findings, an anti-PD-L1 antibody could be used therapeutically to enhance antitumour immune responses in participants with cancer. Results of pre-clinical and clinical studies of monoclonal antibodies (mAbs) targeting the PD-L1/PD-1 pathway have shown evidence of clinical activity and a manageable safety profile, supporting the hypothesis that an anti-PD-L1 antibody could be used to therapeutically enhance antitumour immune response in participants with cancer (Brahmer et al 2012, Hirano et al 2005, Iwai et al 2002, Okudaira et al 2009, Topalian et al 2012, Zhang et al 2008) with responses that tend to be more pronounced in participants with tumours that express PD-L1 (Powles et al 2014, Rizvi et al 2015, Segal et al 2015). In addition, high mutational burden (eg, in bladder carcinoma; Alexandrov et al 2013) may contribute to the responses seen with immune therapy.

In contrast, CTLA-4 is constitutively expressed by regulatory T-cells and upregulated on activated T-cells. CTLA-4 delivers a negative regulatory signal to T-cells upon binding of CD80 (B7.1) or CD86 (B7.2) ligands on antigen-presenting cells (Fife and Bluestone 2008). Blockade of CTLA-4 binding to CD80/86 by anti-CTLA-4 antibodies results in markedly enhanced T-cell activation and antitumour activity in animal models, including killing of established murine solid tumours and induction of protective antitumour immunity. Therefore, it is expected that treatment with an anti-CTLA-4 antibody will lead to increased activation of the human immune system, increasing antitumour activity in participants with solid tumours.

Pre-clinical data have now been added to a wealth of clinical data showing that blockade of negative regulatory signals to T-cells such as CTLA-4 and PD-L1 has promising clinical activity. Ipilimumab was first granted United States (US) FDA approval for the treatment of metastatic melanoma and is currently under investigation for several other malignancies. Nivolumab and pembrolizumab, 2 anti-PD-1 agents, and atezolizumab, an anti-PD-L1 agent, have been granted approvals by agencies for the treatment of a number of malignancies including metastatic melanoma, squamous and non-squamous cell non-small-cell lung cancer, squamous cell carcinoma of the head and neck, and urothelial carcinoma. In addition, there are data from agents in the anti-PD-1/PD-L1 class showing clinical activity in a wide range of tumour types.

2.2.2 Melanoma

Melanoma is the most serious form of skin cancer and the fifth most frequently diagnosed cancer in the US, with 100,350 new cases estimated to occur in 2020, representing 6% of all new cancer diagnoses. The incidence of melanoma is increasing each year. Five-year survival rates depend on the stage of disease at the time of diagnosis. For those with localised disease, 5-year relative survival is estimated at 92%. However, in the US, approximately 4% of patients present with metastatic melanoma, the main cause of melanoma deaths (Zbytek B et al, 2008), and the 5-year relative survival rate is approximately 25%. In 2020, it is anticipated that there will be an estimated 6,850 deaths from melanoma (Siegel RL et al, 2020).

In the US, since 2011, mortality rates for melanoma have declined rapidly, decreasing by an average of approximately 7% per year between 2013 and 2017. This decline in mortality for metastatic disease has been attributed to the approval of immunotherapies such as CPIs and targeted treatments such as BRAF and MEK inhibitors (Siegel RL et al, 2020). Whilst approximately 50% of patients may be suitable for targeted therapy, immunotherapy is the mainstay of treatment, due to the fact that durable CRs and long-term clinical benefit are observed. However, the majority of patients treated with CPI would exhibit either primary resistance (defined as treatment duration ≥ 6 weeks and best response of progressive disease or stable disease for < 6 months), or secondary resistance (defined as treatment duration ≥ 6 months and best response of CR, PR, or stable disease for > 6 months), according to Society for Immunotherapy of Cancer consensus definition (Kluger HM et al, 2020). However, when resistance to CPI occurs on treatment, there are no standards of care and the available treatment recommendation options are limited and provide minimal clinical benefit. Chemotherapy may be an option for these patients but has not been proven to increase survival and is associated with a short-lasting objective response in a minority of patients, as reported in few retrospective studies. The majority of these studies pre-date the use of CPI. However, there are retrospective studies which have reported anecdotal activity of chemotherapy in immunotherapy-resistant patients, with varying magnitudes of benefit (Goldinger DS et al, 2018).

Among the promising treatments for CPI-resistant advanced melanoma there is a cellular therapy with cryopreserved autologous tumour infiltrating lymphocytes (lifileucel or LN144). Preliminary data from a Phase 2 study in patients with unresectable or metastatic melanoma treated with at least 1 systemic prior therapy including a PD-(L)1 blocking antibody and if BRAF V600 mutation positive, a BRAF or BRAF/MEK inhibitor, were recently presented. Sixty-six patients were pre-treated with anti-PD-(L)1, 80% with anti-CTLA-4, and 23% with a combination of BRAF/MEK inhibitor. Common Terminology Criteria for Adverse Events Grade 3/4 thrombocytopenia, anaemia, febrile neutropenia, and neutropenia were reported in 54 (82%), 31 (47%), 36 (55%), and 26 (39%) of the patients respectively. Objective responses were demonstrated in 24 (36.4%) patients and median DoR was not yet reached after 18.7 months of follow-up (Sarnaik A et al, 2020). Considering the proportion of patients with

CTCAE Grade 3/4 events and that patients must have one lesion of > 1.5 cm resectable for tumour-infiltrating lymphocyte generation, it could be anticipated that few patients would be eligible for the treatment with lifileucel. Therefore, patients with advanced unresectable melanoma with primary and secondary resistance to PD-(L)1 inhibition, according to Society for Immunotherapy of Cancer consensus definition (Kluger HM et al, 2020), should be still considered as a population of unmet medical need.

2.2.3 Ceralasertib

Ceralasertib (AZD6738) is being developed as an oral anti-tumour agent in patients with DNA Damage Response (DDR)-deficient tumours, including (but not limited to) breast cancer susceptibility gene (BRCA) mutant and ATM gene or protein deficiency, or in combination with durvalumab, chemotherapy or poly-adenosine 5'-diphosphate-ribose polymerase (PARP) inhibitors. Activity may not be restricted to these patient populations and there is preclinical evidence of activity as monotherapy or combinations across broader malignant disease types and molecular aberrations.

Ceralasertib is an inhibitor of the serine/threonine protein kinase, ATR, a member of the phosphatidylinositol 3 kinase-related kinase family (Foote et al 2018). ATR is the apical kinase in the replication stress response DNA damage induced checkpoint pathway (Cimprich and Cortez 2008, Forment and O'Connor 2018) and during normal DNA replication is recruited at stalled replication forks, which can progress to double strand breaks (DSBs) if left unrepaired. Following resection of DSBs, ATR is recruited to single-strand DNA coated with Replication Protein A following single-strand DNA damage. Recruitment and activation of ATR leads to cell cycle arrest in S-phase while the DNA is repaired, and the stalled replication fork resolved. Loss of ATR function leads to the inability to resolve stalled replication forks, the accumulation of DNA damage and rapid cell death exemplified by nuclear fragmentation.

In addition, there is evidence that ATR can modulate the tumour immune environment and inhibition of ATR can potentiate the effects of treatment by modulation of T-cells. Ceralasertib is being developed as monotherapy in patients whose tumours have potentially sensitising genotypes that include but are not limited to biomarkers such as ATM-deficiency, high replication stress or immune signatures - combining with the PARP inhibitor, olaparib, or chemotherapy where ATR inhibition exacerbates the effects of DNA damaging treatments and in combination with durvalumab where inhibition of ATR is postulated to enhance antitumour activity.

As of the cut-off of 13 June 2021, ceralasertib has been administered to 1173 patients either as monotherapy or in combination with other agents. This includes 506 patients in AstraZeneca sponsored studies (comprising 46 patients treated with monotherapy and 460 patients treated in combination with other agents), 12 patients in AstraZeneca/Acerta sponsored studies and 667 patients in ESR studies.

A detailed description of the chemistry, pharmacology, efficacy, and safety of ceralasertib is provided in the IB.

2.2.4 Durvalumab

Durvalumab is a human monoclonal antibody of the IgG 1 kappa subclass that blocks the interaction of PD-(L)1 (but not programmed cell death ligand-2) with PD-1 on T-cells and CD80 (B7.1) on immune cells. It is being developed by AstraZeneca for use in the treatment of cancer. The proposed MoA for durvalumab is interference in the interaction of PD-(L)1 with PD-1 and CD80 (B7.1). Blockade of PD-(L)1/PD-1 and PD-(L)1/CD80 interactions releases the inhibition of immune responses, including those that may result in tumour elimination. In vitro studies demonstrate that durvalumab antagonises the inhibitory effect of PD-(L)1 on primary human T-cells resulting in the restored production of IFN-γ (Stewart et al, 2015). In vivo studies have shown that durvalumab inhibits tumour growth in xenograft models via a T-cell-dependent mechanism (Stewart et al, 2015). Based on these data, durvalumab is expected to stimulate the patient's antitumour immune response by binding to PD-(L)1 and shifting the balance toward an antitumour response. Durvalumab has been engineered to reduce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity.

As of the DCO date of 12 July 2021, an estimated 12874 patients have received durvalumab in AstraZeneca sponsored interventional studies in multiple tumour types, stages of disease and lines of therapy. Of these, 5136 patients received durvalumab monotherapy. An estimated 13113 patients have been randomised and treated to the various treatment/comparator arms in sponsor-blinded and/or double-blinded studies. In addition, > CCI patients have participated in the durvalumab EAP (Study D4194C00002) for patients with locally advanced, unresectable NSCLC whose disease has not progressed following platinum-based chemoradiation therapy, and > CCI patients in the EAP for durvalumab in combination with platinum and etoposide (Study D419QR00007) for the first-line treatment of extensive-stage small-cell lung carcinoma. The cumulative world-wide post-approval patient exposure since launch is estimated to be approximately 52006 patient-years.

Details on the safety profile of durvalumab monotherapy in Section 2.3.1.2.

Refer to the current durvalumab IB for a complete summary of preclinical and clinical information including safety, efficacy, and PK.

Durvalumab has been approved to treat unresectable stage III non-small cell lung cancer, and extensive-stage small cell lung cancer (administered in combination with chemotherapy). Refer to the package insert (or label) for your specific country, as applicable.

2.2.5 Ceralasertib in Combination with Durvalumab

The underpinning hypothesis for combining durvalumab and ceralasertib 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 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.

Clinical experience of the combination of ceralasertib and durvalumab is summarised in the ceralasertib IB.

Refer to Section 4.3.2 for details.

2.2.6 Biopsy Sub-Study

Emerging studies of DNA damage, genomic instability, and DNA damage repair-deficiencies have been associated with activation of the innate immune response leading to the priming of the adaptive immune system, which may help drive enhanced anti-tumour responses. Pre-clinical evidence suggests that ATR inhibition (such as through ceralasertib treatment) may modulate PD-(L)1 expression and the consequences of the failure to repair S-phase DNA damage (DNA fragmentation, cytosolic DNA/RNA, chromosome mis-segregation, micronuclei, etc) can activate an innate immune response through antiviral nucleic acid sensing pathways. Here, activation of cGAS-STING dependent cytosolic DNA and/or RIG-I-MAVS dependent RNA sensing pathways induce type I IFN signalling and present the cancer cell for T-cell mediated immune destruction, with potential for further enhancement of activity in combination with immune checkpoint inhibition (Sato et al, 2017, Parkes et al, 2017, Sun et al, 2018, Sheng et al, 2020, Feng et al, 2020, AZ unpublished data). In addition to direct activity on cancer cells, ceralasertib shows significant decreases in proliferating CD8+ effector T-cell populations whilst on drug treatment but recovers when treatment is stopped (Krebs et al, 2018) which suggests the importance of sufficient time off drug and utilisation of intermittent dosing schedules to elicit optimal immune-mediated anti-tumour responses.

In pre-clinical studies using mouse tumour models (CCI [redacted]) in immunocompetent mice where ceralasertib and anti-PD-(L)1 show moderate anti-tumour responses as monotherapy, the combination improves anti-tumour activity using an intermittent 1-week

on/1-week off dosing of ceralasertib (See ceralasertib IB primary pharmacodynamics section 2.2.5). Analysis of peripheral blood and tumour immune biomarker profiling (CCI model) of immunocompetent mice dosed with ceralasertib showed marked depletion of proliferating CD8+ T-cells when on-drug (1 week on, compared to baseline) which recovered when off-drug (1 week off), mimicking the impact seen in human clinical trials (Krebs et al, 2018, AZ unpublished data). Moreover, flow cytometry analysis of TILs during the off-drug recovery phase showed re-population of tumour CD8+ T-cells with a significantly increased number with a $PD1^{-}/GzmB^{+}$ phenotype compared to the vehicle control group, suggesting an increased population of effective T-cells in the tumour following ceralasertib treatment using this regimen.

Mechanistic studies in CCI tumour model indicates ceralasertib activity was driven primarily through CCI and CCI-mediated mechanism as anti-tumour responses were suppressed when ceralasertib was co-administered with either anti-CCI or anti-CCI receptor CCI antibodies in immunocompetent mice. Similarly, no anti-tumour activity is observed for this model in immunocompromised nude mice which lack T-cells. The CCI cells treated with ceralasertib also demonstrated CCI and secretion of CCI and CCI genes such as CXCL10/IP10, further supporting ceralasertib induced CCI signalling as potential CCI for immune-mediated cell killing.

Preclinical data suggest that ceralasertib modulates T-cells to immune-effective phenotype, which would sensitise tumour to IO/durvalumab. Evidence of ceralasertib modulating the immune environment is also available from patient data. In an AZ Phase I and Window of opportunity trial, ceralasertib decreased proliferating CD8+ T-cells on-treatment in the tumour and periphery (blood), whereas in the off-drug period the peripheral proliferating T-cells increase to levels higher than baseline. In addition, ceralasertib led to initial decrease of IL12-p40 cytokine followed by a subsequent increase of IL12-p40 subunit in the off-drug period. We have also observed ceralasertib modulating gene expression associated with immune cell subtypes in the tumour. Altogether, the data suggest that ceralasertib modulates the immune environment, which would increase sensitivity of tumour to durvalumab. However, the MoA of ATRi + durvalumab combination is not well understood in patients. The biopsy sub-study will enable understanding of MoA of ATRi + durvalumab and patient selection.

2.3 Benefit/Risk Assessment

2.3.1 Risk Assessment

Monoclonal antibodies directed against immune checkpoint proteins, such as PD-(L)1 as well as those directed against PD-1 or CTLA-4, aim to boost endogenous immune responses directed against tumour cells. By stimulating the immune system, however, there is the potential for adverse effects on normal tissues.

2.3.1.1 Ceralasertib

Data from non-clinical studies and emerging data from the clinical development programme of ceralasertib shows that ceralasertib as monotherapy or in combination with durvalumab has a manageable safety profile in an advanced cancer population. There were no risks identified that would preclude investigation of ceralasertib as monotherapy or in combination with durvalumab in advanced unresectable melanoma.

Identified risks for ceralasertib include anaemia, neutropenia (including febrile neutropenia), thrombocytopenia, nausea, vomiting, diarrhoea, and fatigue/asthenia which have been reported during the clinical use of ceralasertib as monotherapy or in combination with olaparib or durvalumab. Potential risks include myelodysplastic syndrome (MDS)/acute myeloid leukaemia (AML). The emerging safety profile of ceralasertib either as monotherapy or in combination with either olaparib or durvalumab is consistent with preclinical findings and/or the safety profile of the respective combination agent.

Detailed information on the identified and potential risks, including the most commonly observed AEs, for ceralasertib when used alone or in combination are provided in the ceralasertib IB.

2.3.1.2 Durvalumab

Risks with durvalumab include, but are not limited to, diarrhoea/colitis, pneumonitis/interstitial lung disease, endocrinopathies (ie, events of hypophysitis/hypopituitarism, adrenal insufficiency, hyper- and hypo-thyroidism, type I diabetes mellitus and diabetes insipidus), hepatitis/increases in transaminases, nephritis/increases in creatinine, rash/dermatitis (including pemphigoid), myocarditis, myositis/polymyositis, immune thrombocytopenia, infusion-related reactions, hypersensitivity reactions, pancreatitis, encephalitis, serious infections, and other rare or less frequent inflammatory events including neuromuscular toxicities (eg, Guillain-Barré syndrome, myasthenia gravis).

In monotherapy clinical studies, AEs at an incidence of ≥ 20% include events such as fatigue and decreased appetite. Approximately 10% of patients discontinued the drug due to an AE. The majority of treatment-related AEs were manageable, with dose delays, symptomatic treatment, and in the case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated toxicity.

Please see the current version of the IB for a detailed summary of the monotherapy data including AEs, SAEs, and CTCAE Grade 3 to 5 events reported across the durvalumab program.

For information on all identified and potential risks with durvalumab or for a detailed summary of durvalumab monotherapy AE data, refer to the current version of the durvalumab IB.

Table 4 Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Ceralasertib		
Currently identified risks for ceralasertib treatment include anaemia, neutropenia thrombocytopenia, nausea, vomiting, diarrhoea, and fatigue/asthenia. Potential risks for ceralasertib include MDS/AML.	Based on available non-clinical and clinical data and individual case reviews for ceralasertib. For updates on the emerging safety data and a detailed description of all identified and potential risks for ceralasertib please refer to the latest ceralasertib IB (Sections 5.4 to 5.6).	Routine monitoring of haematology and biochemistry blood counts is planned. Dose interruptions and reductions of ceralasertib will be permitted (Section 6.6).
Durvalumab		
Risks with durvalumab include, but are not limited to, diarrhoea/colitis, pneumonitis/ILD, endocrinopathies (ie, events of hypophysitis/hypopituitarism, adrenal insufficiency, hyper- and hypothyroidism, type I diabetes mellitus and diabetes insipidus), hepatitis/increases in transaminases, nephritis/increases in creatinine, rash/dermatitis (including pemphigoid), myocarditis, myositis/polymyositis, immune thrombocytopenia, infusion-related reactions, hypersensitivity reactions, pancreatitis, encephalitis, serious infections, and other rare or less frequent inflammatory events including neuromuscular toxicities (eg, Guillain-Barré syndrome, myasthenia gravis).	In monotherapy clinical studies, AEs at an incidence of ≥ 20% include events such as fatigue and decreased appetite. Approximately 10% of patients discontinued the drug due to an AE. Please see the current version of the IB for a detailed summary of the monotherapy data including AEs, SAEs, and CTCAE Grade 3 to 5 events reported across the durvalumab programme.	Refer to "Dosing Modification and Toxicity Management Guidelines for Durvalumab Monotherapy or in Combination with Other Products" as provided to the investigative site as an Annex document, which is maintained within the Site Master File.

AE = adverse event; AML = acute myeloid leukaemia; CTCAE = Common Terminology Criteria for Adverse Events; IB = Investigator's Brochure; ILD = interstitial lung disease; MDS = Myelodysplastic syndrome; SAE = serious adverse event.

2.3.2 Benefit Assessment

Ceralasertib is considered to have a positive benefit-risk profile for patients with advanced cancer. There are encouraging clinical data of benefit for post-immuno-oncology melanoma patients from ceralasertib plus durvalumab combination. Preclinical and translational data

suggest ceralasertib affects tumour microenvironment, which might make tumour more responsive to durvalumab. Refer to Sections 4.2 and 4.3 for ceralasertib and durvalumab data.

Patients in this study will benefit from the monitoring of all AEs arising during the clinical study, related or not related to the study treatment. In addition, they will be contributing to the development of new therapies for advanced cancer.

The study rationale and dose justification are summarised in Section 2.1 and Section 4.3, respectively.

2.3.3 Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimise risk to patients enrolling in this study, the potential risks identified in association with ceralasertib as monotherapy or in combination with durvalumab are justified by the anticipated benefits that may be afforded to patients with advanced unresectable melanoma.

Further details can be found in the most recent version of the ceralasertib and durvalumab IBs.

3 OBJECTIVES AND ENDPOINTS

Table 5 Objectives and Endpoints for Main Study

Objectives	Endpoints
Primary	
• To estimate the effectiveness of ceralasertib monotherapy and ceralasertib plus durvalumab by assessment of objective response rate (ORR) in patients with unresectable or advanced melanoma and primary or secondary resistance to a PD-(L)1 inhibitor	• ORR is defined as the proportion of patients who have a confirmed complete response, (CR) or confirmed partial response (PR), as determined by Blinded Independent Central Review (BICR) per Response Evaluation Criteria in Solid Tumours (RECIST 1.1) The analysis will include all dosed patients as dosed. Data obtained from randomisation up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of ORR, regardless of whether the patient withdraws from therapy. Patients who go off study treatment without a response or progression, receive a subsequent therapy, and then respond will not be included as responders in the ORR. The primary measure is the estimate of ORR for each experimental treatment arm, and a secondary measure of interest is the odds ratio of the ORR comparing the 2 treatment arms. Additionally, ORR will be analysed using the investigator assessment per RECIST 1.1 as a sensitivity analysis.
Secondary	
• To estimate the effectiveness of ceralasertib monotherapy and ceralasertib plus durvalumab by assessment of Duration of Response (DoR) in patients with unresectable or advanced melanoma and primary or secondary resistance to a PD-(L)1 inhibitor	• DoR will be defined as the time from the date of first documented confirmed response until date of documented progression per RECIST 1.1 as assessed by BICR or death due to any cause The analysis will include all dosed patients as dosed who have a confirmed response, regardless of whether the patient withdraws from study treatment, receives another anti-cancer therapy or clinically progresses prior to RECIST 1.1 progression. The measure of interest is the median and landmark estimates at 6, 9, 12, 15, and 18 months of DoR. Additionally, DoR will be analysed using the investigator assessment per RECIST 1.1 as a sensitivity analysis.

Objectives	Endpoints
• To estimate the effectiveness of ceralasertib monotherapy and ceralasertib plus durvalumab by assessment of time to objective response (TTR) in patients with unresectable or advanced melanoma and primary or secondary resistance to a PD-(L)1 inhibitor	• Time to response is defined as the time from randomisation until the date of first documented objective response, which is subsequently confirmed per RECIST 1.1 as assessed by BICR. The analysis will include all dosed patients as dosed who have a confirmed response. Data obtained from randomisation up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of TTR. Patients who go off treatment without a response or progression, receive a subsequent therapy, and then respond will not be included. The measure of interest is the median TTR and the proportion of patients with response at the first scheduled tumour assessment. Additionally, TTR will be analysed using the investigator assessment per RECIST 1.1 as a sensitivity analysis.
• To estimate the effectiveness of ceralasertib monotherapy and ceralasertib plus durvalumab by assessment of change in target lesion (TL) tumour size in patients with unresectable or advanced melanoma and primary or secondary resistance to a PD-(L)1 inhibitor	• Percentage change from baseline in TL tumour size is based on the RECIST 1.1 TL measurements as assessed by BICR Tumour size is the sum of the longest diameters of the TLs. The percentage change from baseline in TL tumour size at post-baseline assessment (week 16) is obtained for each patient taking the difference between the sum of the TLs at post-baseline assessment and the sum of the TLs at baseline divided by the sum of the TLs at baseline times 100. Patients who progress before week 16 should have had a tumour assessment performed at the time of progression prior to study treatment discontinuation. The tumour size from their latest progression assessment will be used instead of the week 16 assessment for these patients. The analysis will include all dosed patients as dosed. Additionally, best percentage changes from baseline in TL tumour size will be derived. Change in TL tumour size will also be analysed using the investigator assessment per RECIST 1.1 as a sensitivity analysis.

Objectives	Endpoints
• To estimate the effectiveness of ceralasertib monotherapy and ceralasertib plus durvalumab by assessment of progression free survival (PFS) in patients with unresectable or advanced melanoma and primary or secondary resistance to a PD-(L)1 inhibitor	• PFS is defined as time from randomisation until progression per RECIST 1.1 as assessed by BICR or death due to any cause The analysis will include all randomised patients as randomised, regardless of whether the patient withdraws from study treatment, receives another anti-cancer therapy or clinically progresses prior to RECIST 1.1 progression. However, if the patient progresses or dies immediately after 2 or more consecutive missed visits, the patient will be censored at the time of the latest evaluable assessment prior to the 2 missed visits. The measure of interest is the median and landmark estimates at 3, 6, 9, 12 months of PFS, and the hazard ratio comparing the 2 treatment arms. Additionally, PFS will be analysed using the investigator assessment per RECIST 1.1 as a sensitivity analysis.
• To estimate the effectiveness of ceralasertib monotherapy and ceralasertib plus durvalumab by assessment of overall survival (OS) in patients with unresectable or advanced melanoma and primary or secondary resistance to a PD-(L)1 inhibitor	• OS is defined as time from randomisation until the date of death due to any cause The analysis will include all randomised patients as randomised, regardless of whether a patient withdraws from study treatment or receives another anti-cancer therapy. The measure of interest is the median of OS and landmark estimates at 6, 9, 12, and 18 months, and the hazard ratio comparing the 2 treatment arms.
• To assess the PK of ceralasertib alone and when in combination with durvalumab	• Concentration of ceralasertib in plasma (peak and trough concentrations, as data allow; sparse sampling)

Objectives	Endpoints
Safety	
• To assess the safety and tolerability of ceralasertib monotherapy and ceralasertib plus durvalumab in patients with unresectable or advanced melanoma and primary or secondary resistance to a PD-(L)1 inhibitor	Safety and tolerability will be evaluated in terms of adverse events (AEs), vital signs, and clinical laboratory assessments. Assessments related to AEs cover: • Occurrence/Frequency • Relationship to study treatment as assessed by investigator • Common Terminology Criteria for Adverse Events (CTCAE) grade • Seriousness • Death • AEs leading to discontinuation of study treatment • AEs leading to dose reduction of ceralasertib • AEs leading to dose reduction of durvalumab • AEs leading to dose interruption of ceralasertib • AEs leading to dose interruption of durvalumab Vital signs parameters include systolic and diastolic blood pressure, and pulse. Assessments cover: • Observed value • Absolute change from baseline values over time • Vital sign status including change in abnormality (eg, abnormal-clinically significant, abnormal-clinically not significant) from baseline Laboratory parameters include clinical chemistry and haematology parameters as well as urinalysis. Assessments cover: • Observed value • Absolute and percentage change from baseline values over time • Laboratory parameter status including change in abnormality (eg, low, normal, high) from baseline to maximum post-baseline value. Assessments cover: • Urinalysis categorisation as collected on the database including change in categorisation from baseline to maximum on-treatment value
Exploratory	

Objectives	Endpoints
• CCI [redacted]	• CCI [redacted] • CCI [redacted]
• CCI [redacted]	• CCI [redacted]
• CCI [redacted]	• CCI [redacted]
• CCI [redacted]	• CCI [redacted]
• CCI [redacted]	• CCI [redacted]

Objectives	Endpoints
• CCI [redacted]	• CCI [redacted]
• CCI [redacted]	• CCI [redacted]
• CCI [redacted]	• CCI [redacted]

The objectives and endpoints for the biopsy sub-study are as follows:

Table 6 Objectives and Endpoints for the Biopsy Sub-Study

Objectives	Endpoints
Primary	
• To assess changes in CD8+ T-cell infiltration of tumours induced by ceralasertib monotherapy	• CD8+ T-cells tumour infiltration assessed in baseline, on-treatment and off-treatment tumour biopsies Assessments cover: • Observed log_2-transformed value in baseline, on-treatment and off-treatment • Absolute change from baseline in log_2- scale in on-treatment and off-treatment samples • Fold change from baseline for on-treatment and off-treatment samples
Secondary	
• To estimate the effectiveness of ceralasertib plus durvalumab by assessment of ORR, DoR, TTR, change in tumour size, PFS and OS	• As described for the main study, using the investigator assessment of tumour response per RECIST 1.1 The analysis will include all dosed patients as dosed, with endpoints to be derived using date of first dose instead of date of randomisation where applicable.
• To collect tumour tissue samples, or utilise residual samples, for the analysis of tumoural biomarkers that change following treatment with ceralasertib	• Pre-treatment presence and/or on-treatment and/or off-treatment changes in PD-L1 and pRAD50
• To assess changes in the proliferation of carcinoma and/or immune cells within tumours induced by ceralasertib monotherapy	• Proliferation (using Ki67+ marker) of carcinoma and/or immune cells (including CD8+ T cells) will be assessed in baseline, on-treatment and off-treatment tumour biopsies.
Safety	
• To assess the safety and tolerability of ceralasertib plus durvalumab in patients with unresectable or advanced melanoma and primary or secondary resistance to a PD-(L)1 inhibitor	• As described for the main study
Exploratory	
• CCI [redacted]	• CCI [redacted]

Table 6 Objectives and Endpoints for the Biopsy Sub-Study

Objectives	Endpoints
• CCI [redacted]	• CCI [redacted]
• CCI [redacted]	• CCI [redacted]
• CCI [redacted]	• CCI [redacted]

4 STUDY DESIGN

4.1 Overall Design

Main study: This is a Phase 2, randomised, open-label, multicentre, international study assessing the efficacy and safety of ceralasertib and ceralasertib plus durvalumab in patients with unresectable or advanced melanoma and primary or secondary resistance to PD-(L)1 inhibition. Patients will be recruited from multiple centres with a global footprint that is expected to include North America, Europe, and Asia.

Approximately 150 patients will be randomised, at a 2:1 randomisation ratio (approximately 100 patients in Arm 1 and approximately 50 patients in Arm 2) to the following intervention groups:

1 **Arm 1:** Ceralasertib 240 mg BD Days 1 to 7 plus durvalumab 1500 mg Day 8, Q28D, until progressive disease, unacceptable toxicity, withdrawal of consent, or if a study treatment discontinuation criterion is met.
2 **Arm 2:** Ceralasertib 240 mg BD Days 1 to 7, Q28D, until progressive disease, unacceptable toxicity, withdrawal of consent, or if a study treatment discontinuation criterion is met.

Randomisation will be stratified by resistance to prior immune-oncology treatment and baseline LDH expression. At enrolment, investigators will confirm the PD-(L)1 resistance type and whether LDH is normal or above upper limit of normal in order to stratify the patients accordingly. For further details on randomization, refer to Section 6.3.1.

Crossover between treatment arms is not permitted.

Patients must have received at least 1 line of treatment for metastatic disease including an anti-PD1 or anti-PD-(L)1 therapy, or combination of anti-PD1/L1 and anti-CTLA4 and no more than 2 prior regimens in the metastatic setting. All patients must have demonstrated disease progression on anti-PD-(L)1 while on treatment and must have confirmatory scan for progression disease per RECIST 1.1 unless progression is accompanied with clinical deterioration. Patients who progress on adjuvant immunotherapy are also permitted to enrol provided that they progressed on therapy or within 12 weeks after completion of the treatment. Patients with BRAF mutations may have received a BRAF or BRAF plus MEK inhibitor if eligible to do so. All patients must demonstrate disease progression prior to study entry and there must be no intervening therapy eg, investigational agents after completion of prior immunotherapy, except for approved targeted agents for patients with eligible BRAF or c-Kit mutations. For country-specific requirements for France see Appendix K 1.2.

Due to the different schedules of administration of the study treatment options, neither patients nor investigators will be blinded to study treatment assignment. Measures to limit bias are detailed in Section 6.3.

An IDMC comprised of independent experts will be convened to review the unblinded safety and tolerability data and the unblinded efficacy data from the interim analyses and will recommend to the sponsor whether the study should continue unchanged, be stopped, or be modified in any way. Further details on the IDMC are present in Section 9.6.

Number of Patients

Approximately 150 patients are expected to be randomised in total, at a 2:1 randomisation ratio, such that there will be approximately 100 evaluable patients in the ceralasertib and durvalumab combination therapy arm and approximately 50 patients in the ceralasertib monotherapy arm. However, fewer patients may be randomised to any given treatment arm following a recommendation by the IDMC to terminate recruitment to an arm based on safety or lack of efficacy.

Enrolled	Estimated CCI patients
Randomly assigned	Estimated 150 patients
Evaluable patients	Estimated 150 patients

Biopsy sub-study: An open-label, non-randomised, biopsy sub-study is planned in patients suitable for 3 mandatory biopsies. Patients recruited into the biopsy sub-study will receive 1 cycle of ceralasertib monotherapy (Cycle 0) followed by ceralasertib plus durvalumab from Cycle 1.

The biopsy sub-study is anticipated to recruit patients from pre-defined/selected subset of sites and the estimated number of patients in the biopsy sub-study is as follows:

Enrolled	Estimated CCI patients
Evaluable tumour biopsy patients	Estimated 30 patients

Note: “Enrolled” means a patient’s, or their legally acceptable representative’s, agreement to participate in a clinical study following completion of the informed consent process. Potential patients who are screened for the purpose of determining eligibility for the study, but are not randomised/assigned in the study, are considered “screen failures”, unless otherwise specified by the protocol. For country-specific requirements for Germany see Appendix K 1.3.

Serial tumour biopsies are mandated in the patients recruited into the biopsy sub-study and will be taken at baseline during the screening period, during treatment with ceralasertib monotherapy and during the off-treatment period of ceralasertib monotherapy.

During the Cycle 0 treatment period, patients will be treated with ceralasertib 240 mg BD Days 1 to 7, followed by an off-treatment period between Days 8 to 28. From Cycle 1 onwards, patients will be treated with the combination of ceralasertib 240 mg BD Days 1 to 7 plus durvalumab 1500 mg Day 8, Q28D, until progressive disease, unacceptable toxicity, withdrawal of consent, or if a study treatment discontinuation criterion is met.

For dose modification recommendation, stopping rules and discontinuation for ceralasertib monotherapy or in combination with durvalumab, please refer guidance for the main study (Section 6.6).

4.1.1 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 CSP 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 severe acute respiratory syndrome coronavirus 2 [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's ability to conduct the study or the patient's ability to participate in 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, health care provider guidelines (eg, hospital policies) or local government, these changes may include the following options:

- Obtaining consent for the mitigation procedures (note, in the case of verbal consent, the ICF should be signed at the patient's next contact with the study site).
- Rescreening: Additional rescreening for screen failures and to confirm eligibility to participate in the clinical study can be performed in previously screened patients. The investigator should confirm this with the designated AstraZeneca clinical lead.
- Home or Remote visit: Performed by a site-qualified HCP or HCP provided by a TPV.
- Telemedicine visit: Remote contact with the patients using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

If a site visit is not possible, at home delivery and administration of study treatment may be performed.

For further details on study conduct during civil crisis, natural disaster, or public health crisis, refer to Appendix H.

4.2 Scientific Rationale for Study Design

Two separate investigator-initiated collaborative studies support the investigation of ceralasertib in advanced unresectable malignant melanoma. The first study was the combination with weekly paclitaxel in 33 PD-1 resistant advanced melanoma patients which showed an ORR of 33% median PFS of 3.6 months and median OS of 7.4 months. Seven out of 11 patients had a duration of response of more than 6 months (Lee J et al, 2020). The second study, a combination of ceralasertib with durvalumab in 30 post PD-1 patients with advanced melanoma, showed a ORR of 30%, six of nine patients with a PR maintained a response for > 6 months (66.7%), median DoR 8.8 months, median PFS 7.1 months and median OS 14.2 months (Kim R et al, 2022) (Section 4.3). The patient population in both of these studies was patients with advanced unresectable malignant melanoma with primary or secondary resistance to anti-PD-(L)1 inhibition, who demonstrated anti-tumour activity and were a population with unmet medical need, similar to patients with early relapse following adjuvant therapy. AstraZeneca aims to confirm the efficacy signals in a multicentre company-sponsored trial.

Secondly, given that there is no single agent data for ceralasertib in advanced unresectable malignant melanoma and activity was demonstrated for 2 separate ceralasertib combinations, AstraZeneca aims to test the activity of monotherapy ceralasertib to understand the contribution of ceralasertib to the combination with durvalumab. Thus, a 2-arm trial is proposed comprising ceralasertib plus durvalumab and ceralasertib monotherapy.

In this study, durvalumab is not proposed to be tested as a single agent as it is not the standard of care in the treatment of advanced melanoma. Durvalumab (10 mg/kg) has been evaluated in a Phase 1 study (unpublished data on file) in 21 stage IV PD-(L)1 naïve patients with advanced cutaneous melanoma; 6 out the 21 patients were previously treated with immunotherapy and in this study, 3 (14%) patients achieved a PR and 9 patients had stable disease as best response. The proportion of patients with DoR ≥ 6 months was 3 (100%); ≥ 9 months, 2 (67%); and ≥ 12 months, 1 (33%). Among the 3 patients with PR, 2 were previously treated with only ipilimumab monotherapy, one in the adjuvant setting with progressive disease as best response and the second in the setting of advanced unresectable metastatic melanoma.

Therefore, due to the available evidence, durvalumab monotherapy is anticipated to have low clinical efficacy in patients with confirmed progression on prior anti-PD-(L)1 regimens in a patient population in need of an effective disease controlling regimen.

4.3 Justification for Dose

The ceralasertib and durvalumab combination therapy doses and regimen selected for this study are based on the goal of selecting an optimal combination dose that would demonstrate promising efficacy and have an acceptable safety profile.
The rationale is based on the emerging efficacy data and improved tolerability from Module 3 of HUDSON study (D6185C00001), which included patients with NSCLC who previously progressed on chemotherapy and immune checkpoint inhibitors. In HUDSON study, ceralasertib 240 mg BD was administered using a 7-day schedule, Days 22 to 28, combined with durvalumab 1500 mg on Day 1, in a 28-day cycle. The combination was more effective than other durvalumab combinations in patients within the same study, with superior PFS and OS data. Furthermore, emerging pre-clinical data and preliminary peripheral blood biomarker data from PKPD modelling in Study 4 (D5330C00004) are more supportive for the 7 days schedule, showing that a longer time off ceralasertib treatment allows for a more immune permissive environment and reduced haematological toxicity.

4.3.1 Ceralasertib Monotherapy Dose Rationale

The dose of ceralasertib selected for this study (240 mg BD) is primarily based on the clinical results observed in the HUDSON study (D6185C00001), with supportive data on preclinical, translational and clinical pharmacology data/modelling from Study 4 (D5330C00004).

Preliminary PK observations from Study 4 (D5330C00004) showed CCI dose-proportional increase in exposure, where the plasma concentrations following a single dose at 320 mg QD were CCI to that observed at 240 mg QD CCI % overlap in AUC), suggesting the need to change to BD schedules in order to increase ceralasertib exposure beyond the dose of 240 mg QD.

The dose of ceralasertib as monotherapy 240 mg BD for 7 days in 28-day cycles is based on clinical safety and tolerability (mainly bone marrow safety outcomes) and clinical PK/PD data. The dose level of 240 mg BD is predicted to maintain ceralasertib concentrations above the estimated concentration of an inhibitor where ATR catalytic activity is reduced by 90% (IC90) threshold for CCI hours in CCI % of the patients based on simulations from a preliminary population PK model, and hence, it achieves maximum IC90 daily coverage. In addition, 1-week ceralasertib dosing maximises cytotoxic T-cell (CD8+/Ki67+) proliferative burst (by minimising the time in which proliferative T-cells are depleted) during the three-week off-treatment period, potentially promoting upregulation of PD-(L)1 which can be subsequently blocked with durvalumab to enhance anti-tumour T-cell responses.

Considering emerging PK data from ongoing studies, there is no evidence to indicate any ethnic sensitivity in Asian patients compared to Western patients.

The choice of ceralasertib schedule is supported by preclinical data in syngeneic mouse tumour models in which an intermittent dosing schedule for ceralasertib is most efficacious in terms of balancing the direct anti-tumour effects, the potential for priming an IFN-mediated immune response and dynamic modulation of the tumour immune microenvironment (see ceralasertib IB). An intermittent schedule is also supported by a population PK-PD model describing ceralasertib-induced thrombocytopenia and neutropenia, which showed that at least two-week off-treatment period is needed for platelet/neutrophil recovery. This same model also demonstrated that haematological toxicity is reduced with a 7-day schedule compared to 14-day schedule of ceralasertib.

The immunomodulatory effects of ceralasertib have been evaluated in multiple clinical studies. Longitudinal peripheral blood analysis from Study 4 (D5330C00004) and Study 7 (D5330C00007) demonstrated on-drug suppression of peripheral proliferating cytotoxic T-cells (CD8+/Ki67+) during ceralasertib treatment, followed by off-drug rebound above pre-treatment levels. Similar changes were not seen in total T-cells (proliferating cytotoxic T-cells comprise a subset of the total T-cells), suggesting that these effects are primarily restricted to proliferating cells. In addition, 1-week ceralasertib dosing maximises cytotoxic T-cell (CD8+/Ki67+) proliferative burst (by minimising the time in which proliferative T-cells are depleted) during the three-week off-treatment period, potentially promoting upregulation of PD-L1 which can be subsequently blocked with durvalumab to enhance anti-tumour T-cell responses.

Ceralasertib has been tested as monotherapy in the investigator-initiated collaborative study-PATRIOT (D533OC00002, Study NCT02223923), which showed that the tolerable schedule is 2 weeks on/2 weeks off in a 28-day cycle (Dillon et al, 2017; Dillon et al, 2019). Ceralasertib is also being tested as monotherapy in patients with ATM gene or protein altered advanced solid tumours and prostate cancer in the modular Phase 2A study PLANETTE (Study D5339C00001).

Refer to the current ceralasertib IB for further information.

4.3.2 Ceralasertib and Durvalumab Combination Therapy Dose Rationale

The ceralasertib and durvalumab combination therapy doses and regimen selected for this study are based on the goal of selecting an optimal combination dose that would demonstrate promising efficacy and have an acceptable safety profile.

To date, ceralasertib has been tested at different dose levels (80 mg to 240 mg BD) in combination with durvalumab in two ongoing AZ-sponsored clinical studies and seven externally sponsored studies, across multiple therapy indications. Ceralasertib 240 mg 14-day regimen (Days 15 to 28) in combination with durvalumab 1500 mg on Day 1, of a Q28D cycle is being tested in Module 3 of the ongoing Study 4 (D5330C00004) where 27 patients with

NSCLC and squamous cell cancer of the head and neck have been treated. The ceralasertib and duvalumab combination is also being tested in the HUDSON study (D6185C00001) in NSCLC with 2 various schedules of ceralasertib 7 days or 14 days. In HUDSON the 7 days schedule was well tolerated and demonstrated encouraging efficacy data in 66 patients.

Longitudinal peripheral gene expression data from the HUDSON study (D6185C00001) indicate increases in gene expression signatures associated with Tumour Necrosis Factor α (TNFα) signalling and CD56dim Natural Killer (NK) cells upon treatment with ceralasertib, which return to baseline during the off-drug period. T-cell receptor sequencing, assessed using Adaptive Biotechnologies' immunoSEQ assay, revealed increases in peripheral richness following treatment with the combination of ceralasertib and durvalumab. Taken together, these data support a mechanism of immune modulation by ceralasertib in combination with durvalumab in this patient population.

Clinical data has emerged that supports the 7-day schedule of ceralasertib in NSCLC. The HUDSON study is exploring ceralasertib 240 mg BD in both a 7-day schedule (in Module 3) and a 14-day schedule (in Module 9) combined with durvalumab 1500 mg QD, Day 1 in a Q28D cycle. The 240 mg BD 14-day schedule of ceralasertib was also explored in Study 4 Module 3 (D5330C00004C). Safety information from HUDSON Module 3 and Module 9 and Study 4 (D5330C00004) indicate that a 7-day schedule has better tolerability in NSCLC patients than a 14-day schedule. The 14-day schedule is associated with increased dose reductions (n=9/25 [36%]; compared to HUDSON patients on the 7-day schedule, n=9/65 [14%]) and increased dose discontinuations due to AEs (n = 6/25 [24%] in Study 4; compared to HUDSON patients on the 7-day schedule, n=3/65 [5%]). The combination of ceralasertib and durvalumab showed OS benefit in patients on the 7-day schedule. In Module 3 of HUDSON, ceralasertib 240 mg BD was administered Days 1 to 7 at Cycle 0, and from Cycle 1 durvalumab 1500 mg Day 1 was combined with ceralasertib 240 mg BD Days 22 to 28. This dose and schedule were well tolerated. The efficacy data from HUDSON Module 3 showed ORRs of 28.6% (ATM deficient cohort [A.3.ATM]), 8.0% (acquired resistance cohort [B.3.ACQ]), and 15.0% (primary resistance cohort [B.3.PRI]). Six-month mPFS was 69.64% (A.3.ATM), 35.19% (B.3.ACQ) and 45.59% (B.3.PRI). The 6-month median OS was 95.24% (A.3.ATM), 76.0% (B.3.ACQ) and 70.0% (B.3.PRI). Efficacy data for the dose-expansion cohort in Study 4 (D5330C00004) is immature as the study is ongoing. However, there is preliminary evidence of efficacy for the combination of ceralasertib and durvalumab in 4 patients in the dose-escalation part of the study; these 4 patients achieved a confirmed RECIST response (n=1 confirmed complete response and n=3 partial responses)

A recent study (D6183C00003, NCT03780608) conducted in a single centre in South Korea investigated the activity of ceralasertib plus durvalumab in a Phase 2 study in patients with advanced unresectable melanoma resistant to prior anti-PD-(L)1 treatment. The dose of ceralasertib was 240 mg BD, Days 15 to 28, in combination with durvalumab, 1500 mg QD,

Day 1, Q28D. The data indicated there were 9 patients (30%, 95% CI 13.6% - 46.4%) with ORR, and a DCR of 63.3% (95% CI 28% 46.1% - 80.6%) patients with DoR > 6 months, median DoR 8.8 months (range, 3.8 to 11.7 months). After 18 PFS events, median PFS 7.1 months (95% CI 3.6 - 10.6; 67% mature), and median OS 14.2 months (95% CI 9.3-19.1 months). Responses were seen across the melanoma subtypes suggesting that this combination has broad activity in malignant melanoma. In terms of safety, TEAEs led to dose reduction of ceralasertib in 14 patients (46.7%). The most common causes of ceralasertib dose reduction were thrombocytopenia (Grade > 3) and neutropenia (Grade > 3). None of the patients discontinued durvalumab or ceralasertib due to AEs (Kim R et al, 2022).

In the proposed Phase II melanoma study, a 7-day dosing schedule for the ceralasertib dose of 240 mg BD, in combination with 1500 mg durvalumab on Day 8 of a 28-day cycle will be used, based on supportive preclinical, translational, clinical pharmacology, and clinical data.

4.3.2.1 Dose Rationale for Durvalumab 1500 mg Q28D

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.

A comparison of the observed durvalumab peak and trough concentrations following an initial dose of 10 mg/kg, 20 mg/kg and a fixed dose of 1500 mg revealed the geometric mean peak concentration at 1500 mg was 13% higher than at 20 mg/kg and 149% higher than that of 10 mg/kg. The fixed dose of 1500 mg Q4W is predicted to result in a similar AUC with only a modest difference in median peak and trough levels at steady state compared to 10 mg/kg q2w, based on population PK simulations. Complete PD-(L)1 suppression is anticipated following a 1500 mg Q4W dose, given its equivalent PK exposure (AUC, maximum observed concentration [C_{max}], and trough) at steady state compared to the 20 mg/kg Q4W dose. Therefore, the fixed dose of 1500 mg Q4W has been selected as the dosing regimen investigated in multiple ongoing studies of durvalumab across different cancer types.

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 mAbs 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 the expectation of similar PK exposure and variability, AstraZeneca considered it feasible to switch to fixed dosing regimens.

A fixed dose of 1500 mg durvalumab administered Q28D is to be used for all patients with a body weight greater than 30 kg.

Currently, the use of a fixed dose of 1500 mg durvalumab, administered both in combination with chemotherapy and as monotherapy, is approved for treatment of extensive stage small cell lung cancer; additionally, the 1500 mg fixed dose is approved in some countries as monotherapy for unresectable stage III non-small cell lung cancer. Refer to the local package insert (or label) for current approved regional dosing regimens, as applicable.

4.4 End of Study Definition

For the purpose of Clinical Trial Transparency, 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 define two completion dates:

Primary Completion Date – the date that the final patient 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 patient 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 patient's last visit), whether the clinical study concludes according to the pre-specified protocol or is terminated.

A patient is considered to have completed the study if they have completed all phases of the study including the last visit or the last scheduled procedure shown in the SoA (Section 1.3).

The study may be stopped if, in the judgement of AstraZeneca, study patients are placed at undue risk because of clinically significant findings.

The end of the study is defined as the date of the last visit of the last patient in the study globally.

See Section 6.7 for details on patient management following final DCO as well as following study completion.

5 STUDY POPULATION

The target population of interest in this study is patients with unresectable or advanced melanoma with resistance to PD-(L)1 inhibition.

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

Patients who do not meet the eligibility criteria requirements are screen failures; refer to Section 5.4.

5.1 Inclusion Criteria

5.1.1 Main Study and Biopsy Sub-Study

Patients are eligible to be included in the study only if all of the following criteria apply:

Informed Consent

1 Capable of giving signed informed consent as described in Appendix A which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

2 Provision of signed and dated written CCI [redacted] informed consent prior to collection of samples for CCI [redacted] that supports CCI [redacted]

Age

3 Patient must be ≥ 18 years of age inclusive, at the time of signing the informed consent.

Type of Patient and Disease Characteristics

4 Patient must have a histologically or cytologically confirmed diagnosis of unresectable or metastatic melanoma of cutaneous, acral or mucosal subtype.

5 Availability of an archival tumour sample and a fresh tumour biopsy taken at screening, if medically feasible as per investigator assessment. If a mandatory fresh biopsy is not feasible, the patient is permitted to enrol if they have an archival sample up to 5 years.

6 Patient must have received at least 1 prior immunotherapy (anti-PD-(L)1 ± anti-CTLA-4) for a minimum of 6 weeks and no more than 2 prior regimens in the metastatic setting. Patients must have confirmed progression during treatment with a PD-(L)1 inhibitor +/- a CTLA-4 inhibitor, eg, nivolumab, pembrolizumab, or atezolizumab, or the combination

of nivolumab and ipilimumab. Confirmed progression is defined as radiologic progression confirmed by a second scan at 4 to 12 weeks after the initial scan showing disease progression or, a single scan showing radiological progression accompanied by correlative symptoms suggestive to disease progression. Patients who received adjuvant therapy for previously resected disease with PD-(L)1 agents may also be eligible if disease recurrence occurred while still receiving the anti-PD-(L)1 therapy or < 12 weeks from the last dose of the anti-PD-(L)1 therapy.

7 No intervening treatment eg, investigational therapy is permitted between the anti-PD-(L)1 therapy and study treatment. However, patients with BRAF or c-Kit mutations that are eligible for targeted treatment, may receive the targeted treatment before or after licensed anti-PD-(L)1 therapy and prior to study entry. For country-specific requirements for France see Appendix K 1.2.

8 The interval between the last dose of anti-PD-(L)1, BRAF/MEK inhibitor and the first dose of the study regimen must be a minimum of 14 days.

9 BRAF V600E or V600K mutation status must be known at screening. Patients with BRAF mutant melanoma may have had a prior treatment regimen that included vemurafenib, dabrafenib, or an approved BRAF and approved MEK inhibitor. For country-specific requirements for France see Appendix K 1.2.

10 May have received a TKI (eg, imatinib) if c-kit mutant and available, or declined therapy.

11 Eastern Cooperative Oncology Group performance status 0 or 1, with no deterioration over the previous 2 weeks prior to baseline or day of first dosing.

12 Measurable disease by RECIST 1.1. At least 1 lesion, not previously irradiated, that qualifies as a RECIST 1.1 target lesion (TL) at baseline and can be accurately measured at baseline as ≥ 10 mm in the longest diameter (except lymph nodes, which must have short axis ≥ 15 mm) with CT or MRI and is suitable for accurate repeated measurements. Tumour assessment by CT scan or MRI must be performed within 28 days prior to randomisation. Cutaneous lesions and other superficial lesions are not considered measurable disease lesions but may be considered as non-target lesions. **For patients in the main study:** if the patient has only 1 measurable lesion per RECIST 1.1, the biopsy specimen should be obtained from the non-target lesion or archival tissue.

13 Patients with known CNS lesions should be asymptomatic, adequately treated with stereotactic radiation therapy, craniotomy, gamma knife therapy, or whole brain radiotherapy, with no subsequent evidence of CNS progression; patients must not require steroid exceeding > 10 mg prednisone or equivalent; patients with a history of central nervous system metastases must have MRI of the brain at screening. All AEs while receiving prior immunotherapy must have completely resolved, be medically controlled, or resolved to baseline prior to screening for this study.

14 Patients must have a life expectancy ≥ 3 months from proposed first dose date.

Weight

15 Body weight above 30 kg (> 30 kg).

Sex/Reproduction

16 Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies (Section 5.3.1).

(a) Male patients: Male patients who intend to be sexually active with a female partner of childbearing potential must be surgically sterile or using an acceptable method of contraception (see Section 5.3.1) from the time of screening throughout the total duration of the study and for 6 months after the last dose of the study treatment, in order to prevent pregnancy in a partner. Male patients must not donate or bank sperm during this same time period. For country-specific requirements for Belgium and France see Appendices K 1.1 and K 1.2, respectively.

(b) Female patients:

(i) Negative pregnancy test (serum) for women of childbearing potential.

(ii) Women of childbearing potential must agree to use one highly effective method of birth control (Table 7) from enrolment throughout the study until 6 months after the last dose of study treatment. Non sterilised male partners of a woman of childbearing potential must use a male condom plus spermicide (condom alone in countries where spermicides are not approved) throughout this period. For country-specific requirements for Belgium and France see Appendices K 1.1 and K 1.2, respectively.

(iii) Female patients must not breastfeed and must not donate or retrieve ova from signing ICF to approximately 6 months after the last dose of study treatment.

5.1.2 Biopsy Sub-Study

Patients are eligible to be included in the biopsy sub-study only if they meet all of the inclusion/exclusion criteria of the main study and all of the following criteria:

1 Consent to the provision of 3 mandatory tumour biopsies.

2 Have at least 1 tumour lesion medically accessible for 3 biopsies at baseline, on ceralasertib treatment and off ceralasertib treatment.

Accessible lesions are defined as tumour lesions which are amenable to biopsy, unless clinically contraindicated or the patient has withdrawn consent. It is preferable that the same lesion is used for each biopsy, but if this is not possible, a patient may enrol if they have more than 1 lesion that is suitable for biopsy from the same tissue type eg, 3 cutaneous lesions.

3 Lesions used for biopsy should be different from those used as RECIST lesions, unless there are no other lesions suitable for biopsy.

4 Lesions used for biopsy may have received prior radiation therapy only if there is documented evidence of progression in the lesion after radiation treatment.

5.2 Exclusion Criteria

5.2.1 Main Study and Biopsy Sub-Study

Patients are excluded from the study if any of the following criteria apply:

Medical Conditions

1 Patients must not have experienced a toxicity that led to permanent discontinuation of prior CPI treatment. Patients with unresolved ≥ Grade 2 toxicity from prior treatment (except alopecia and vitiligo) or ≥ Grade 1 for anti-PD-(L)1 antibody-related immune-mediated toxicities are excluded. Patients with irreversible toxicity that is not reasonably expected to be exacerbated by treatment with durvalumab or ceralasertib may be included (eg, hearing loss) after consultation with the AstraZeneca study clinical lead.

2 As judged by the investigator, any evidence of diseases (such as severe or uncontrolled systemic diseases, including uncontrolled hypertension, active bleeding diseases, active infection, active interstitial lung disease/pneumonitis, serious chronic gastrointestinal conditions associated with diarrhoea, psychiatric illness/social situations), history of allogenic organ transplant, which, in the investigator's opinion, makes it undesirable for the patient to participate in the study or that would jeopardise compliance with the protocol.

3 Refractory nausea and vomiting, chronic gastrointestinal disease, inability to swallow a formulated product, or previous significant bowel resection that would preclude adequate absorption, distribution, metabolism, or excretion of study treatment.

4 History of another primary malignancy except for malignancy treated with curative intent with no known active disease ≥ 3 years before the first dose of study treatment and of low potential risk for recurrence, basal cell carcinoma of the skin, squamous cell carcinoma of the skin or lentigo maligna that has undergone potentially curative therapy or adequately treated carcinoma in situ without evidence of disease.

5 Uveal melanoma (eg, choroidal, iris, and ciliary body).

6 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 an endocrine AE of Grade ≤ 2 are permitted to enrol if they are stably maintained on appropriate replacement therapy and are asymptomatic.

7 History of symptomatic congestive heart failure, unstable angina pectoris, uncontrolled cardiac arrhythmia (multifocal premature ventricular contractions, bigeminy, trigeminy,

ventricular tachycardia), which is symptomatic or requires treatment (CTCAE Grade 3), symptomatic or uncontrolled atrial fibrillation despite treatment, or asymptomatic sustained ventricular tachycardia. Patients with atrial fibrillation controlled by medication or arrhythmias controlled by pacemakers may be permitted upon discussion with the study clinical lead.

8 Investigator judgment of 1 or more of the following:

(a) Mean resting corrected QT interval of > 470 ms.

(b) History of QT prolongation associated with other medications that required discontinuation of that medication, or any current concomitant medication known to prolong the QT interval and cause Torsades de Pointes (TdP).

(c) Congenital long QT syndrome, family history of long QT syndrome, or unexplained sudden cardiac death under 40 years of age in first-degree relatives.

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

10 Active or prior documented autoimmune or inflammatory disorders (including, but not limited to inflammatory bowel disease [eg, colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], celiac disease, irritable bowel disease, Wegner syndrome, Hashimoto syndrome, hyperthyroidism, Sjogren's syndrome, glomerulonephritis, multiple sclerosis, vasculitis, rheumatoid arthritis, idiopathic pulmonary fibrosis, pneumonitis, organising pneumonia, hepatitis, sarcoidosis, active tuberculosis) within the past 3 years.

11 History of organ transplant that requires use of 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. Use of immunosuppressive medications for the management of study treatment-related AEs is acceptable. In addition, use of inhaled, topical and intranasal steroids, and local steroid injections (eg, intra-articular injection) is permitted. Steroids as premedications for hypersensitivity reactions or as an anti-emetic (eg, CT scan premedication) are also permitted.

12 Inadequate bone marrow and impaired hepatic or renal function as demonstrated by any of the following laboratory values:

- Haemoglobin < 9.0 g/dL (no transfusions within the last 28 days).
- Absolute neutrophil count < 1.5 x 10^9/L.
- White blood cells ≤ 3 x 10^9/L.
- Platelet count < 100 x 10^9/L.
- Albumin < 33 g/L.

- Total bilirubin ≥ 1.5 × the ULN or ≥ 3 × ULN in the presence of documented Gilbert's syndrome (unconjugated hyperbilirubinemia).
- Aspartate aminotransferase/transaminase (SGOT)/Alanine aminotransferase/transaminase (ALT) (SGPT) ≥ 2.5 x institutional ULN unless liver metastases are present in which case it must be ≥ 5 x ULN.
- Serum creatinine > 1.5 x institutional ULN.
- Calculated creatinine clearance (CrCL) < 45 mL/min as determined by Cockcroft-Gault (using actual body weight).

  Males:

  $$\text{CrCL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}}$$

  Females:

  $$\text{CrCL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}} \times 0.85$$

- International normalised ratio ≥ 1.5 or other evidence of impaired hepatic synthesis function. Patients on warfarin may participate in this study but it is recommended that their INR is monitored more frequently.

13 Known active infection requiring systemic therapy, active hepatitis infection, positive hepatitis C virus antibody, hepatitis B virus surface antigen or HBV core antibody (anti-HBc), at screening. Patients with a past or resolved HBV infection (defined as the presence of anti-HBc and absence of HBsAg) are eligible. Patients positive for HCV antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

14 Patients with confirmed COVID-19 infection by PCR test who have not made a full recovery.

15 Known history of testing positive for human immunodeficiency virus (positive HIV 1/2 antibodies) or known acquired immunodeficiency syndrome.

16 Known history of drug or alcohol abuse within 21 days of screening.

Prior/Concomitant Therapy

17 Patients who have received prior chemotherapy for advanced melanoma are excluded.

18 Any concurrent anticancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (eg, hormone replacement therapy) is allowed.

19 Palliative radiotherapy with a limited field of radiation within 2 weeks or with wide field of radiation or to more than 30% of the bone marrow within 4 weeks before the first dose of study treatment.

20 Major surgical procedure or significant traumatic injury within 4 weeks of the first dose of study treatment or an anticipated need for major surgery during the study. Note: Local surgery of isolated lesions for palliative intent is acceptable.

21 Receipt of:

(a) Live or live attenuated vaccine within 30 days prior to the first dose of study treatment

(b) COVID-19 vaccine (regardless of vaccine delivery platform, eg, vector, lipid nanoparticle) 30 days prior to the date of randomisation (from last vaccination or booster dose).

Prior/Concurrent Clinical Study Experience

23 Patients with a known hypersensitivity to ceralasertib or durvalumab or any of the excipients of the study treatment.

24 Patients who have received prior durvalumab, regardless of the tumour type that is being treated, are excluded.

25 Patients who have received Chk1 or ATR inhibitor are excluded.

26 Participation in another clinical study with an investigational product administered in the last 28 days or 5 half-lives, whichever is shorter.

Other Exclusions

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

28 Judgement by the investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions, and requirements.

29 Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 1 month after the last dose of ceralasertib (for ceralasertib monotherapy) and 3 months after the last dose of study treatment for durvalumab and ceralasertib combination therapy. For country-specific requirements for Belgium and France see Appendices K 1.1 and K 1.2, respectively.

5.2.2 Biopsy Sub-Study

1 Patients must comply with the exclusion criteria described for the main study.

2 Patients with evidence of bleeding disease deemed unsafe for serial biopsies.

5.3 Lifestyle Considerations

5.3.1 Contraception

Male patients:

Non-sterilised male patients (including males sterilised by a method other than bilateral orchidectomy, eg, vasectomy) who intend to be sexually active with male partners and women of non-child bearing potential must be using an acceptable method of contraception such as

male condom plus spermicide (condom alone in countries where spermicides are not approved) from the time of screening throughout the total duration of the study and for 1 week after the last dose of study treatment to prevent exposure to ceralasertib via the semen. Where a sexual partner of a male patient is a 'woman of childbearing potential' who is not using effective contraception, or who is already pregnant, then the male patient must use a condom plus spermicide (where approved), during the study and for a further 6 months after the last dose of study treatment to prevent pregnancy in a partner. Male patients should refrain from fathering a child or donating sperm from the start of dosing until 6 months after the last dose of study treatment, if there is a concern about damaging the developing foetus from drug in ejaculate. For country-specific requirements for Belgium and France see Appendices K 1.1 and K 1.2, respectively.

Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception.

Vasectomised males are considered fertile and should still use a male condom plus spermicide as indicated above during the clinical study.

Female partners (of childbearing potential) of male patients must also use a highly effective method of contraception throughout this period (Table 7).

Female patients:

- Women not of childbearing potential are defined as women who are surgically sterile (ie, complete hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal.
- Women will be considered postmenopausal if they have been amenorrhoeic for 12 months prior to the planned date of randomisation without an alternative medical cause. The following age-specific requirements apply:
  - Women < 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all hormonal replacement therapy and if they have luteinising hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution.
  - Women ≥ 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all hormonal replacement therapy, or had radiation-induced menopause with last menses > 1 year ago, or had chemotherapy-induced menopause with last menses > 1 year ago.
- Women of childbearing potential must use highly effective form of birth control, as defined in Table 7, from the time of signing the informed consent and for 6 months after the last dose of study treatment. For all women of childbearing potential, cessation of contraception after the above defined time point should be discussed with a responsible

physician. For country-specific requirements for Belgium and France see Appendices K 1.1 and K 1.2, respectively.

A highly effective method of contraception is defined as one that can achieve a failure rate of 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). Female condom and male condom should not be used together. All women of child-bearing potential must have a negative serum pregnancy test result at Visit 1.

Table 7 Highly Effective Methods of Contraception (< 1% Failure Rate)

Non-hormonal methods	Hormonal methods
• Total sexual abstinence (evaluate in relation to the duration of the clinical study and the preferred and usual lifestyle choice of the patient) • Vasectomised sexual partner (with patient assurance that partner received post-vasectomy confirmation of azoospermia) • Tubal occlusion • Intrauterine device (provided coils are copper-banded)	• Injection: Medroxyprogesterone injection (eg, Depo-Provera®) [aa] • Levonorgestrel-releasing intrauterine system (eg, Mirena®) [aa] • Implants: Etonogestrel-releasing implants (eg, Implanon® or Norplant®) • Intravaginal devices: Ethinylestradiol/etonogestrel-releasing intravaginal devices (eg, NuvaRing®) • Combined pill: Normal and low dose combined oral contraceptive pill • Patch: Norelgestromin/ethinylestradiol-releasing transdermal system (eg, Ortho Evra®) • Mini pill: Progesterone based oral contraceptive pill using desogestrel: Cerazette® is currently the only highly effective progesterone-based pill

[a] Hormonal methods not prone to drug-drug interactions.

5.3.2 Meals and Dietary Restrictions

Patients must fast (water to drink only) from at least 2 hours prior to taking a dose of ceralasertib to at least 1-hour post-dose for all doses.

Patients should avoid concomitant drugs, energy drinks, herbal supplements and/or ingestion of foods known to modulate CCI activity (Appendix F).

5.3.3 Skin

During study treatment and for 4 weeks after the last dose of study treatment, patients should be advised to avoid prolonged exposure to the sun, wear protective clothing including a hat, sunglasses, and seek shade from the sun as much as possible; in addition, SP30+ sunscreen should be used. Exposure to other sources of ultraviolet light including sun beds and tanning booths, etc, should be avoided.

5.3.4 Blood Donation

Patients should not donate blood or blood components while participating in this study and through 90 days after receipt of the final dose of study treatment or until alternate anti-cancer therapy is started.

5.4 Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened following consultation with the sponsor. Rescreened patients should be assigned the same patient number (ie, E-code) as for the initial screening. However, rescreening should be documented so that its effect on study results, if any, can be assessed. All assessments must be repeated for rescreening unless they are within 21 days of randomisation (> 28 days may be required for biopsy collection) or as applicable as some screening assessments could be valid for more than 21 days.

If a patient is screened initially for the biopsy sub-study and is considered ineligible and is subsequently rescreened for the main study, the patient number will change.

These patients should have the reason for study withdrawal recorded in eCRF as “eligibility criteria not fulfilled” (ie, patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (ie, patients who are not randomised/entered in the study).

Patient enrolment and randomisation are described in Section 6.3.

6 STUDY TREATMENT

Study treatment is defined as any investigational treatment(s), marketed product(s) or placebo intended to be administered to a study patient according to the study protocol.

6.1 Study Treatments Administered

6.1.1 Study Treatments

AstraZeneca will supply ceralasertib and durvalumab as study treatment.

Table 8 Investigational Products

Treatment name	Ceralasertib	Durvalumab
Type	Synthetic	Biologic
Dosage form	Tablet	Concentrate solution for infusion
Unit dose strength(s)	Tablets in either 120 mg or 80 mg	500 mg (50 mg/mL)
Dosage regimen	240 mg BD for 7 consecutive days (Days 1 to 7); Q28D	1500 mg on Day 8 of each 28-day cycle; 20 mg/kg in patients who weigh ≤ 30 kg
Route of administration	Oral	IV infusion
Use	Experimental	Experimental
IMP and NIMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and labelling	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 labelling. Label text will be translated into local language, as required.	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.

Note: Label text prepared for durvalumab will show the product name as “MEDI4736” or “durvalumab” depending upon the agreed product name used in the approved study master label document. All naming conventions are correct during this transitional period.
BD = twice daily; IMP = investigational medicinal product; IV = intravenous; NIMP = non-investigational medicinal product; Q28D = every 28 days.

6.1.1.1 Ceralasertib

Ceralasertib tablets will be supplied by AstraZeneca.

For storage and administration of ceralasertib, see Section 6.2.2.

6.1.1.2 Durvalumab

Durvalumab will be supplied by AstraZeneca as a concentrate for solution for infusion. Durvalumab 500 mg will be supplied in a vial containing 50 mg/mL durvalumab, 26 mM histidine/histidine hydrochloride, 275 mM trehalose dihydrate and 0.02% weight/volume

(w/v) polysorbate 80; the solution has a pH of 6.0 and density of 1.05 g/mL. The label-claim volume for durvalumab is 10 mL.

Durvalumab is a sterile, clear to opalescent, colourless to slightly yellow solution, free from visible particles.

6.2 Preparation/Handling/Storage/Accountability

1 The investigator or designee (eg, pharmacist) must confirm appropriate temperature conditions have been maintained during transit for all study treatment received at the site and throughout the entire study duration until authorisation is provided for on-site destruction or removal of the study treatment, reflecting completion of the study. In the event of a temperature excursion detected at any time during the study, sites will follow the reporting procedures for notifying the sponsor (or designated party); release of study treatment for clinical use can only occur once the event has been reviewed and approval is provided by the sponsor (or designated party).

2 Only patients enrolled in the study may receive study treatment and only authorised site staff may prepare, supply or administer study treatment. All study treatment 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.

3 The investigator is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records reflecting destruction or return of all unused study treatment); this task may be delegated to study staff members identified on the site delegation log. The investigator (or designee) is also responsible for ensuring that the patient has returned all unused study treatment.

4 Further guidance and information for the final disposition of unused study treatments are provided in the Study Reference Manual.

6.2.1 Durvalumab Storage, Infusion Preparation and Administration

6.2.1.1 Durvalumab Storage

Durvalumab vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. The investigator, or an approved representative (eg, pharmacist), will ensure that all study treatment is stored in a secured area, in refrigerated temperatures (2°C to 8°C; 36°F to 46°F) and in accordance with applicable regulatory requirements. A temperature log will be used to record the temperature of the storage area. Temperature excursions outside the permissible range listed in the clinical supply packaging are to be reported to the monitor upon detection. A calibrated temperature monitoring device will be used to record the temperature conditions in the drug storage facility. Storage conditions stated in the IB may be superseded by the label storage.

Study treatment must be kept in original packaging until time of preparation to prevent prolonged light exposure.

The dose of durvalumab must be prepared by the investigator's or site's designated study treatment manager using aseptic techniques. Total time from needle puncture of the study treatment vial to the start of administration must 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 must not exceed 24 hours otherwise a new dose must be prepared from new vials. Durvalumab vials do not contain preservatives; any unused portion of the vial must be discarded immediately after use.

6.2.1.2 Durvalumab Infusion Preparation

A dose of 1500 mg for patients > 30 kg in weight will be prepared using an IV bag containing 0.9% sodium chloride for injection or 5% dextrose for injection, with a final durvalumab concentration ranging from 1 to 15 mg/mL. Add 30 mL (ie, 1500 mg) of durvalumab to the IV bag. The IV bag size should be selected 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 weight falls to 30 kg or below (≤ 30 kg) the patient should receive weight-based dosing equivalent to 20 mg/kg of durvalumab Q28D (IV bag size selected is such that the final concentration is within 1 to 15 mg/mL) after consultation between investigator and study clinical lead, until the weight improves to > 30 kg, at which point the patient should start receiving the fixed dosing of durvalumab 1500 mg Q28D.

6.2.1.3 Durvalumab Administration

Durvalumab infusions are to be administered through an IV administration set with a 0.2 or 0.22 μm filter; acceptable configurations include an IV set containing an in-line filter or the attachment of a separate filter to the distal end of the IV tubing.

The durvalumab infusion time is 1 hour ± 10 minutes; however, if there are interruptions, the total allowed time must not exceed 8 hours with the infusion bag maintained at room temperature, otherwise a new dose must be prepared from new vials.

Do not co-administer other drugs through the same infusion line.

The IV line will be flushed according to local practices to ensure the full dose is administered. Infusion time does not include the final flush time.

6.2.2 Ceralasertib Storage and Administration

6.2.2.1 Ceralasertib Storage

Ceralasertib product label on the bottle specifies the appropriate storage. It must be stored in the original outer container and under conditions specified on the label.

6.2.2.2 Ceralasertib Administration

Ceralasertib tablets should be taken with a glass of water. When ceralasertib is administered, patients must fast (water permitted) for at least 2 hours prior to taking a dose, to at least 1 hour post-dose for all doses.

Ceralasertib will be administered orally 240 mg twice daily, approximately 12 ± 2 hours apart, starting on Day 1 until Day 7, in each treatment cycle of both the treatment arms in the main study. In the biopsy sub-study, patients will self-administer ceralasertib tablets from Day 1 until Day 7 of Cycle 0, followed by no study treatment between Day 8 and Day 28, and from Day 1 until Day 7 Cycle 1 onwards.

Patients must receive ceralasertib for 7 days within each 28-day cycle. A cycle must not be < 28 days. Ceralasertib 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 Days 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 of ceralasertib dosing in the particular cycle. Dosing after Cycle Day 7 is not permitted and 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 the interval between two doses is more than 14 hours, then 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.

6.3 Measures to Minimise Bias: Randomisation and Blinding

6.3.1 Main Study

This is an open-label study; potential bias will be reduced by the following steps: central randomisation, use of BICR for tumour assessments and use of IDMC (Section 9.6).

For the main study, patients will be randomly allocated to receive 1 of the study treatments, at a 2:1 randomisation ratio, such that there will be approximately 100 evaluable patients in the ceralasertib and durvalumab combination therapy arm and approximately 50 patients in the ceralasertib monotherapy arm.

At enrolment, Investigators will confirm PD-(L)1 resistance type and whether the LDH is normal or above upper limit of normal in order to stratify the patients accordingly.

Stratification factors include:

1 Resistance to prior immune-oncology treatment (primary/early relapse in adjuvant setting vs secondary resistance). Based on SITC (Kluger HM et al, 2020) definitions of resistance to PD-(L)1 therapy:
Primary resistance: patients with a drug exposure of ≥ 6 weeks who had PD or stable disease for < 6 months.
Secondary resistance: patients with a drug exposure of ≥ 6 months who had confirmed CR or PR, or SD for > 6 months
Early relapse in adjuvant setting: patients with PD within 12 weeks of the last dose
2 Baseline lactate dehydrogenase expression (below and equal to the upper limit of normal vs above upper limit of normal). Lactate dehydrogenase will be determined by a local test and values can vary depending on the lab. Therefore, patients will be stratified for LDH normal or above upper limit of normal, according to local lab reference ranges.

Patients will be randomised as they become eligible. Once the eligibility of a patient has been confirmed, the investigator (or designee) will notify the centralised IWRS (all patients). The IWRS will then provide the randomisation identification code. Randomisation should take place as close to the start of study treatment as possible (randomisation does not apply to patients in the biopsy sub-study).

Due to the different schedules of administration of the treatment options, neither patients nor investigators will be blinded to treatment assignment. However, to limit bias to study conduct, data quality, data analyses and data interpretation, appropriate key personnel and certain functions at AstraZeneca will remain blinded to treatment allocation until the database lock at primary analysis. Separate unblinded counterparts eg, biostatisticians and statistical programmers will do all necessary unblinded work during the course of the study, including interaction with the IDMC. Detailed procedures for maintenance of the blind will be described in the IDMC Charter and the study integrity plan.

Study treatment details are summarised in Section 6.

6.3.1.1 Screening Procedures

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

Investigators should keep a record (ie, the patient screening log) of patients who entered screening.

At screening/baseline (Days -21 to -1), the investigators or suitably trained delegate will:

- Obtain signed informed consent before any study-specific procedures are performed. If laboratory or imaging procedures were performed for alternate reasons prior to signing consent, these can be used for screening purposes with consent of the patient. However, all screening imaging results must have been obtained within 28 days of randomisation and all screening laboratory results within 21 days of randomisation.
- Identify patients to the IWRS per country regulations. Obtain a unique 7-digit enrolment number (E-code), through the IWRS in the following format (ECCNNXXX: CC being the country code, NN being the centre number, and XXX being the patient enrolment code at the centre). This number is the patient's unique identifier and is used to identify the patient on the eCRFs.
- Determine patient eligibility (see Sections 5.1 and 5.2).
- Obtain signed informed consent for genetic research study (optional). Patients who decide not to sign the specific genetic ICF but the general study ICF are eligible for study enrolment and all other study procedures.

If the patient is ineligible and not randomised, the IWRS should be accessed to terminate the patient in the system.

Patients will begin treatment on Day 1. Treatment should start no more than 3 working days after being randomised. Patients must not be randomised and treated unless all eligibility criteria have been met.

6.3.1.2 Methods for Assigning Treatment Groups

The actual treatment given to patients will be determined by the randomisation scheme in the IWRS. The randomisation scheme will be produced by a computer software programme that incorporates a standard procedure for generating randomisation numbers. One randomisation list will be produced for each of the randomisation strata. A blocked randomisation will be generated, and randomisation will be balanced within the IWRS at the site/country/region/central level. All centres will use the same list in order to minimise any imbalance in the number of patients assigned to each treatment group.

Randomisation codes will be assigned strictly sequentially, within each stratum and site/country/region, as patients become eligible for randomisation. The IWRS will provide the kit identification number to be allocated to the patient at the randomisation visit and subsequent treatment visits.

6.3.1.3 Procedures for Handling Incorrectly Enrolled or Randomised Patients

Patients who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Patients who are

enrolled but subsequently found not to meet all the eligibility criteria must not be randomised or started on study treatment and must be withdrawn from the study.

Where a patient does not meet all the eligibility criteria but is randomised in error, or incorrectly started on treatment, the investigator should inform the AstraZeneca study clinical lead immediately, and a discussion should occur between the AstraZeneca study clinical lead and the investigator regarding whether to continue or discontinue the patient from treatment. The AstraZeneca study clinical lead must ensure all decisions are appropriately documented and that the potential benefit/risk profile remains positive for the patient.

6.3.2 Biopsy Sub-Study

Enrolment to the biopsy sub-study will be open at selected sites only. At these sites, when enrolment to the biopsy sub-study is open, patients who are eligible for the biopsy sub-study should be enrolled to the biopsy sub-study part and not be randomised into the main study.

6.4 Treatment Compliance

Sites will follow local practices for verification of study treatment doses, prepared and administered to study patients.

When the individual dose for a patient is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.

When patients are dosed at the site, they will have study treatment prepared, dispensed and administered by the investigator or designee, under medical supervision. The date, and time if applicable, of dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of study treatment and study patient identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.

When patients self-administer study treatments at home, compliance with study treatment will be assessed once per cycle and per local institutional policy. Compliance will be assessed by direct questioning, counting returned study treatments, etc during the site visits and documented in the source documents and eCRF. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

For ceralasertib, dosing compliance will be reviewed with the patient at the beginning of each new treatment cycle when study treatment is dispensed. All patients will be required to complete a dosing diary using an electronic device. The dosing diary must be reviewed once per each cycle and per local institutional policy. The patient must be instructed to record each date and time the dose(s) were taken in the dosing diary. If a dose is missed, the reason must be noted in the diary.

A record of the number of ceralasertib tablets dispensed to and taken by each patient must be maintained and reconciled with study treatment and compliance records. Study treatment start and stop dates, including dates for treatment delays and/or dose reductions will also be recorded in the eCRF.

The investigator is responsible for ensuring that the patient has returned all unused study treatment.

6.5 Concomitant Therapy

Any concomitant treatment, procedure, or other medication considered necessary by the investigator for the patient's safety and wellbeing, or vaccine (including over-the-counter or prescription medicines, vitamins, and/or natural/herbal products, other "folk remedies", etc) or other specific categories of interest that the patient is receiving at the time of enrolment or receives during the study, including the follow-up period following the last dose of study treatment must be recorded in the eCRF along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

If medically feasible, patients must abstain from taking prescription or non-prescription drugs (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or [redacted] half-lives (whichever is longer) before the start of study treatment until completion of the follow-up visit, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

Paracetamol/Acetaminophen, at doses of ≤ 2 grams/day, is permitted for use any time during the study. Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the Medical Monitor if required.

6.5.1 Restricted, Prohibited, and Permitted Concomitant Medications/Therapies

Restricted, prohibited, and permitted concomitant medications/therapies are described below. Refer also to the dose modification guidelines for management of study treatment-related toxicities in the Annex document to this CSP.

Table 9 Restricted Medications/Therapies

Medication/class of drug/Therapy	Usage (including limits for duration permitted and special situations in which it's allowed
Hormonal therapy	For non-cancer-related conditions (eg, insulin for diabetes and hormone replacement therapy) only.
Bisphosphonates	For the treatment of bone metastases and osteoporosis.
Corticosteroids	For the treatment of specific adverse drug reactions (refer to Toxicity Management Guidelines document).

Table 10 Prohibited Concomitant Medications

Prohibited medication/class of drug	Usage
Any investigational therapy including anti-cancer therapy other than those under investigation in this study	Must not be given concomitantly while the patient is on study treatment
mAbs against CTLA-4, PD-1, or PD-(L)1 other than those under investigation in this study	Must not be given concomitantly while the patient is on study treatment
Any concurrent treatment including chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study, except for those medications identified as "restricted", as listed above.	Must not be given concomitantly while the patient is on study 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])
Live attenuated vaccines	Must not be given while receiving study treatment and up to 30 days after the last dose of durvalumab or ceralasertib. Local guidance should be consulted to determine the acceptable timeframe for vaccine administration following chemotherapy study treatment.
Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumour necrosis factor-α blockers	Must not be given concomitantly or used for premedication prior to the IO infusions. The following are allowed exceptions: • Use of immunosuppressive medications for the management of study treatment-related AEs • Short-term premedication for patients receiving combination agent 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). Consult

Table 10 Prohibited Concomitant Medications

Prohibited medication/class of drug	Usage
	with study clinical lead for prolonged therapy or need for a slow taper.
Herbal and natural remedies that may have immune-modulating effects and interfere with interpretation of study results	Must not be given concomitantly unless agreed by the sponsor.
Sunitinib	Must not be given concomitantly or through 90 days after the last dose of durvalumab.
EGFR TKIs	Must not be given concomitantly. Must 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 first generation EGFR TKIs) has been reported when durvalumab has been given concomitantly.

AE = adverse event; CTLA-4 = cytotoxic T-lymphocyte associated antigen; EGFR = epidermal growth factor receptor; IO = immune-oncology; mAbs = monoclonal antibodies; PD-1 = programmed cell death-1; PD-(L)1 = programmed cell death ligand-1; TKI = tyrosine kinase inhibitor.

Premedication

- **Anti-emetic treatment:** No primary prophylactic treatment with anti-emetics is advised. However, anti-emetic treatment may be administered as secondary prophylaxis or treatment according to the guidelines of the participating sites. Please note: aprepitant (Emend®) is a substrate, moderate CCI of CCI and also an CCI of CCI.

Therefore, the use of aprepitant is NOT allowed in this study for the treatment of nausea and vomiting induced by the study treatment. In general, drugs that interfere with CCI are not allowed in this study, and aprepitant is NOT an exception.

Supportive care

Patients may receive concomitant medications or treatments (eg, acetaminophen or diphenhydramine), except for those medications identified as "prohibited," as listed above, if the investigator deems it necessary to provide adequate AE management.

Patient may receive vaccines limited only to non-live attenuated preparations (eg, influenza vaccine).

Patients will be permitted to receive appropriate supportive care measures (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy, etc]) as deemed necessary by the treating physician, including but not limited to the items outlined below:

- **Diarrhoea:** Diarrhoea should be treated promptly with appropriate supportive care, including administration of an anti-diarrhoeal agent according to standard practice guidelines. Anti-diarrhoeal agents should not be taken prophylactically. Patients should be instructed to begin taking anti-diarrhoeal medication at the first sign of: 1) poorly formed or loose stool, 2) occurrence of more bowel movements than usual in one day or 3) unusually high volume of stool. Anti-diarrhoeal agents should be deferred if blood or mucus is present in the stool or if diarrhoea is accompanied by fever. In this setting, appropriate diagnostic microbiologic specimens should be obtained to exclude an infectious aetiology. Patients should also be advised to drink liberal quantities of clear fluids to help prevent dehydration.
- **Nausea/vomiting:** Nausea and vomiting should be treated adequately, and strong consideration should be given to the administration of secondary prophylactic anti-emetic therapy according to standard institutional practice. Patients should be strongly encouraged to maintain liberal oral fluid intake. Supportive care with aprepitant (a CCI) according to institutional guidelines in the context of standard of care chemotherapy is NOT allowed.
- **Anaemia:** Transfusions and/or erythropoietin may be utilised as clinically indicated for the treatment of anaemia but should be clearly noted as concurrent medications. No blood transfusions in the 28 days prior to first dose is allowed.
- **Neutropenia:** Colony-stimulating factors including G-CSF, pegylated G-CSF or GM-CSF according to Institutional Standards, following discussion with the Principal Investigator and AstraZeneca.

Avoid concomitant medications, herbal supplements and/or ingestion of foods that significantly modulate CCI activity. Note these include common azole antifungals, macrolide antibiotics, etc. For patients receiving study treatment in the absence of discontinuation criteria, if the investigator feels that concomitant administration of

medications, herbal supplements or foods that significantly modulate CCI activity is necessary based upon medical judgement, such products may be administered with caution following discussion between the investigator and the sponsor Study Physician.

The AstraZeneca study clinical lead should be contacted if there are any questions regarding concomitant or prior therapy.

If any concomitant therapy is administered due to new or unresolved AE, it should be recorded.

Patients must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.

6.5.2 Drug-Drug Interaction Between Ceralasertib and Other Drugs

Ceralasertib 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 CCI and transporter inhibitors/inducers, and CCI and transporter substrates are available in Appendix F. They are not exhaustive and the absence of a drug from these lists does not imply that its combination with ceralasertib is safe. If ceralasertib is being administered in combination, potential interactions of the combination partner should also be considered.

Restrictions regarding drugs affecting CCI metabolism
The principal enzyme for metabolising ceralasertib is CCI. Patients should avoid concomitant drugs, herbal supplements, and/or ingestion of foods known to modulate CCI activity from the time they enter the screening period until 28 days after the last dose of study treatment.

- Prior to study treatment, use of potent inducers or inhibitors of CCI are not permitted. For patients taking any of these drugs (examples provided in Appendix F) the required washout periods before starting ceralasertib is CCI half-lives; except for CCI, which is 3 weeks.
- On study treatment, if there is no suitable alternative concomitant medication other than a potent inhibitor of CCI, the investigator must interrupt ceralasertib for the duration of the potent CCI inhibitor and wait for the required washout period (CCI half-lives) before dosing ceralasertib again. If potent CCI inducers are considered necessary for the patient's safety and welfare, this may diminish the clinical efficacy of ceralasertib and the patient should be monitored carefully for any change in the efficacy of study treatment. Refer to Appendix F for additional guidance.

- The use of any herbal supplements or 'folk remedies' (and medications and foods that significantly modulate CCI 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 ceralasertib may be metabolised by CCI but a lesser extent, therefore caution should be applied with co-administration of potent inhibitors or inducers of CCI (examples provided in Appendix F).

Drugs known to be inhibitors or inducers of CCI and/or CCI, undertake appropriate monitoring if co-administration is necessary

- Ceralasertib is also a CCI substrate. Co-administration of CCI inhibitors or inducers may affect exposure to ceralasertib and therefore, they should not be co-administered with ceralasertib. If the use of any inhibitors or inducers of CCI are considered necessary for the patient's safety and welfare, the investigator must interrupt ceralasertib for the duration of the CCI inhibitor or inducer and wait for the required wash-out period of the CCI modulator (CCI half-lives) before dosing ceralasertib again. Refer to Appendix F for additional guidance.
- Ceralasertib is a substrate of CCI. Co-administration of strong CCI inhibitors or inducers may affect exposure to ceralasertib; therefore, it is recommended that the investigators must interrupt ceralasertib for the duration of the strong CCI inhibitor or inducer and wait for the required washout period of the CCI modulator (CCI half-lives) before dosing ceralasertib again.

Drugs known to be substrates of CCI, and/or CCI, undertake appropriate monitoring if co-administration is necessary

Based on in vitro data, ceralasertib is a potential inhibitor of CCI as well as an inducer of CCI. Caution should be applied with co-administration of drugs that are either completely metabolised by CCI or that are substrates of CCI and also have a narrow therapeutic index. Investigators should be aware that the exposure of other drugs metabolised by CCI may be increased, and exposure of other drugs metabolised by CCI may be reduced.

Drugs known to be substrates of CCI and CCI, undertake appropriate monitoring if co-administration is necessary

Ceralasertib is an inhibitor of CCI and CCI. Caution should be applied with co-administration of substrates of CCI and/or CCI as ceralasertib may increase their exposure.

CCI therapy

Patients on CCI may participate in this study but it is recommended that their INR is monitored more frequently.

Refer to Appendix F for further details regarding prohibited concomitant medications with ceralasertib.

6.5.3 Drug-Drug interactions Between Durvalumab and Other Drugs

There is no information to date on drug-drug interactions with durvalumab either pre-clinically or in patients.

As durvalumab is a mAb and therefore a protein, it will be degraded to small peptides and amino acids and will be eliminated by renal and reticuloendothelial clearance (CL). It is therefore not expected that durvalumab will induce or inhibit the major drug metabolising CCI pathways. As a result, there are no expected PK drug-drug interactions. The mechanism of action of durvalumab involves binding to PD-(L)1, and therefore significant pharmacodynamic drug interactions with commonly administered concomitant medications are not expected.

6.5.4 Rescue Medication

The study site will supply the required rescue medication and it will be obtained locally. The following rescue medications are required to be available at the site:

1 Infliximab/infliximab biosimilar (eg, for colitis).
2 Mycophenolate (eg, for hepatitis).

Under certain circumstances when local sourcing by the study site is not feasible or local regulations prevent the use of infliximab or mycophenolate for this use (as they are considered off-label for management of immunotherapy related toxicities), AstraZeneca will centrally supply the required rescue medications, which will be labelled and accompanied by Prescribing Information with local language translated text in accordance with regulatory guidelines. Accountability and storage requirements, as specified in Section 6.2, apply for any study treatment supplied by AstraZeneca. If required to manage an imAE, then the IVRS/IWRS will allocate the specific medication either by a kit or another identification number, to the pharmacist for a specific patient at the time of the event.

The date of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

As a result of imAEs that could potentially be experienced by patients on durvalumab and ceralasertib, appropriate treatment (eg, steroids and specific immunosuppressant rescue medications) must be made readily available to this patient population.

6.6 Dose Modification

Patients may delay durvalumab dosing under certain circumstances.

- Dosing may be delayed per the Dosing Modification and Toxicity Management Guidelines, due to either an immune or a non-immune-related AE.
- If dosing must be delayed for reasons other than treatment-related toxicity, dosing will resume as soon as feasible.
- Dosing intervals of subsequent cycles may be shortened as clinically feasible in order to gradually align treatment cycles with the schedule of tumour efficacy (RECIST) and PRO assessments.

Any clinically significant and/or unacceptable toxicity observed during the course of the study should be managed in the first instance by interruption of the dose of study treatment, dose reductions if necessary, and administration of supportive therapy.

If the toxicity resolves or reverts to ≤ CTCAEv5 Grade 1 or 2 (depending on the toxicity) treatment with study treatment may be restarted using the rules in Table 11 and Table 12 for dose modifications for ceralasertib plus durvalumab and ceralasertib monotherapy, respectively. Patients who have 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.

Patients who develop a ≥ Grade 3 of anaemia, neutropenia, or thrombocytopenia during the treatment period will also need to have additional assessments on Day 7 (for ceralasertib monotherapy) and on Day 15 (for combination of ceralasertib and durvalumab and for those in the biopsy sub-study) until there is no evidence of ≥ Grade 3 anaemia, neutropenia, or thrombocytopenia for at least 2 cycles.

If the toxicity does not resolve to ≤ CTCAEv5 Grade 1 or 2 (depending on the toxicity) or the patient is not showing clinical benefit, then the patient should be discontinued from study treatment and observed until resolution of the toxicity.

For simultaneous toxicities (for example, anaemia and neutropenia), the event should be considered singular, and CCI further dose modification should be made providing that both CCI resolve within CCI. However, sequential toxicities (for example, anaemia followed by neutropenia) should follow the guidance as show in Table 11 and Table 12; if a recent dose reduction has been made, a second modification may be required before beginning the next cycle.

CCI dose interruptions are allowed as required for a maximum of CCI on each occasion as recommended in Table 11. If the duration of ceralasertib dose interruption is longer than CCI, the case should be discussed with the AstraZeneca study physician.

Once dose is reduced, escalation is not permitted.

Study treatment dose interruption for conditions other than CCI resolution should be kept as CCI as possible. If a patient cannot restart study treatment within CCI for resolution of intercurrent conditions not related to disease progression or CCI, the case should be discussed with the AstraZeneca Study Physician.

No CCI of study treatment is required for any CCI procedure unless deemed necessary by the physician. Study treatment should be CCI for a minimum of CCI before a patient undergoes palliative radiation treatment or planned surgery. Study treatment should be CCI within CCI as long as any bone marrow toxicity has recovered. Radiotherapy should not involve CCI and progressive disease should be CCI.

The dose of study treatment must not be adjusted under any other circumstances 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 11 Guidance for Dose Modifications, Interruptions, and Discontinuations for Ceralasertib (all treatment arm) and Ceralasertib plus Durvalumab

Event	Action
CCI	

Table 11 Guidance for Dose Modifications, Interruptions, and Discontinuations for Ceralasertib (all treatment arm) and Ceralasertib plus Durvalumab

Event	Action
CCI	

Table 12 Dose Reduction Levels for Ceralasertib

CCI

6.6.1 Management of Toxicities

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

- Treat each of the toxicities with maximum supportive care (including holding 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 treatment 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 National Cancer Institute CTCAE, version 5.0.

Comprehensive TMG have been developed to assist investigators with the recognition and management of toxicities associated with use of the immune-checkpoint inhibitor, durvalumab, PD-(L)1 inhibitor. These guidelines are applicable when durvalumab is used in combination with other anticancer drugs (ie, antineoplastic chemotherapy, targeted agents) administered concurrently or sequentially as part of a protocol-specific treatment regimen. The TMGs provide information for the management of immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions that may be observed with checkpoint inhibitor monotherapy or combination checkpoint inhibitor regimens, with specific instructions for checkpoint inhibitor-specific dose modifications (including discontinuation) and treatment interventions. Investigators are advised however to use local practice guidelines and consult local references for the management of toxicities observed with other anti-cancer treatment.

The most current version of the TMGs is provided to the investigative site as an Annex to Protocol document entitled, “Dosing Modification and Toxicity Management Guidelines (TMGs) for Durvalumab Monotherapy or in Combination with Other Products” and is maintained within the Site Master File.

Patients should be thoroughly evaluated, and appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAEs. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an immune-related adverse events diagnosis. In the absence of a clear alternative aetiology, events should be considered potentially immune-related. In addition, there are certain circumstances in which durvalumab and ceralasertib should be permanently discontinued (see Section 7.1 for discontinuation criteria and the Dosing Modification and Toxicity Management Guidelines). Following the first dose of study treatment, subsequent administration of durvalumab can be modified based on toxicities observed as described in the Dosing Modification and TMG. These guidelines have been prepared by the sponsor to assist

the investigator in the exercise of his/her clinical judgement in treating these types of toxicities. These guidelines apply to AEs considered causally related to durvalumab monotherapy and durvalumab with ceralasertib regimen by the reporting investigator.

For patients who weigh > 30 kg, the dose of durvalumab cannot be modified. In case of doubt, the investigator should consult with the Study Physician. If a patient's body weight falls to 30 kg or 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 5.0. Dose reductions of durvalumab are not permitted. In case of doubt, the investigator should consult with the Study Physician.

Management of prolonged haematological toxicities

Patient should be referred to a haematologist for further investigations and management in the event of prolonged haematological toxicity such as:

- ≥ 2-week interruption/delay in study intervention due to CTCAE Grade 3 or worse anaemia and/or development of blood transfusion dependence
- ≥ 2-week interruption/delay in study intervention due to CTCAE Grade 3 or worse neutropenia (ANC < 1×10^9/L)
- ≥ 2-week interruption/delay in study intervention due to CTCAE Grade 3 or worse thrombocytopenia and/or development of platelet transfusion dependence (Platelets < 50×10^9/L)

Consider checking weekly differential blood counts including reticulocytes and peripheral blood smear. Bone marrow analysis and/or blood cytogenetic analysis should be considered at this stage according to standard haematological practice.

Study intervention should be discontinued if blood counts do not recover to CTC Grade 1 or better within 4 weeks of dose interruption.

Development of a confirmed myelodysplastic syndrome or other clonal blood disorder should be reported as an SAE and full reports must be provided by the investigator to AstraZeneca Patient Safety. Study intervention should be discontinued if patient's diagnosis of MDS and/or AML is confirmed.

The dose reduction levels for ceralasertib are summarised in Table 12.

6.7 Treatment After the End of the Study

As described in Section 4.4, the study will remain open until all patients have discontinued study treatment and completed their last expected visit/contact.

After the final DCO for this study, AstraZeneca will continue to supply open-label ceralasertib or ceralasertib plus durvalumab to patients in the continued access phase of the study (PTAP) until disease progression occurs as judged by the investigator or until meeting any other discontinuation criteria as defined in Section 7.1. Patients should be followed according to the institution's Medical Standard of Care and as deemed appropriate by the investigators. No further data collection is required, except for SAEs and AEs, if applicable. Refer to Section 8.3.11 for safety reporting during PTAP.

For patients continuing in the PTAP, it is recommended that the patients continue the scheduled site visits and investigators continue to observe ongoing patients at the frequency employed prior to the primary DCO. Investigators will monitor the patients' safety laboratory results prior to and periodically during treatment with durvalumab and ceralasertib in order to manage AEs in accordance with the durvalumab and ceralasertib Dosing Modification and Toxicity Management Guidelines (see the Annex document to this CSP).

During the PTAP, while a patient is receiving ceralasertib or ceralasertib plus durvalumab, dose modification and stopping criteria should generally follow the approach as described in this protocol. A change in the dose/schedule of ceralasertib or ceralasertib plus durvalumab should only occur for safety reasons, based on the investigator's judgement.

In the event that a roll-over or safety extension study is available at the time of the final DCO and database closure, patients currently receiving treatment with ceralasertib or ceralasertib plus durvalumab may be transitioned to such a study, and the current study would reach its end. The roll-over or extension study would ensure treatment continuation with visit assessments per its protocol, as applicable. Any patients who would be eligible to move to such a study would be given a new informed consent, as applicable.

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, where possible.

7 DISCONTINUATION OF STUDY TREATMENT AND PATIENT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Treatment

It may be necessary for a patient to permanently discontinue (definitive discontinuation) study treatment. Patients may be withdrawn from any aspect of the study at any time, without prejudice to further treatment. If study treatment is permanently discontinued, the investigator should instruct the patient to contact the site before or at the time if study treatment is stopped. A patient that decides to discontinue study treatment will always be asked about the reason(s) and the presence of any AEs. The reason for discontinuation should be documented in the source document and the appropriate section of the eCRF. See the SoA (Section 1.3) for data to be collected at the time of discontinuation of study treatment and follow-up and for any further evaluations that need to be completed.

Patients who have permanently discontinued from further receipt of study treatment will need to be discontinued from the IVRS/IWRS. All study treatment should be returned by the patient at their next on-site study visit or unscheduled visit.

Patients will be discontinued from study treatment in the following situations:

- Clinical or RECIST 1.1-defined radiological progression (refer to Section 8.1.1 and Appendix G).
- Investigator determination that the patient is no longer benefiting from study treatment.
- An AE that, in the opinion of the investigator or AstraZeneca:
  - Contraindicates further dosing.
  - Meets criteria for discontinuation defined in the dose modification guidelines for management of study treatment-related toxicities (see the Annex document to this CSP).
  - Presents life-threatening circumstances or causes unacceptable toxicity to the patient.
- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment. A patient who discontinues treatment is normally expected to continue to participate in the study (eg, for safety and survival follow-up) unless they specifically withdraw their consent to all further participation in any study procedures and assessments (see Section 7.2).
- Severe non-compliance with the CSP as judged by the investigator or AstraZeneca.
- Pregnancy or intent to become pregnant.
- Initiation of subsequent anticancer therapy, including another investigational agent.

- Patients incorrectly initiated on study treatment.
  - When the reason does not impact safety consider the risk/benefit to the patient of stopping study treatment.
- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study.
- A decision on the part of the sponsor to suspend or discontinue development of the drug for reasons including but not limited to unfavourable risk/benefit or change in drug development plan.

Note that discontinuation from study treatment is NOT the same thing as a withdrawal from the study.

For country-specific requirements for France see Appendix K 1.2.

7.1.1 Temporary Discontinuation/Rechallenge

The rules for restarting study treatment are summarised in Section 6.6.

7.1.2 Follow-up of Patients Post Discontinuation of Study Treatment

After study treatment discontinuation, all patients will be followed up for safety assessments 30 days after their last dose of study treatment for ceralasertib monotherapy or 180 days after last dose of study treatment for ceralasertib and durvalumab combination (ie, the safety follow-up visit). Patients will also be followed for survival status and post discontinuation anti-cancer therapies. Additional assessments to be performed at the time of the safety follow-up are detailed in the SoA (Section 1.3). For country-specific requirements for Belgium and France see Appendices K 1.1 and K 1.2, respectively.

Patients who have discontinued study treatment prior to objective RECIST 1.1-defined radiological progression will be followed up with tumour assessments according to the SoA until RECIST 1.1 defined disease progression or death regardless of whether or not the patient started a subsequent anti-cancer therapy, unless they have withdrawn all consent to study related assessments.

7.1.3 Follow-up for Survival

Patients will be followed up for survival status, as indicated in the SoA (Section 1.3), starting at an 8-weekly time interval, reducing to 12 weekly after 18 months. Survival information will be obtained via telephone contact with the patient or the patient's family, or by contact with the patient's current physician.

7.2 Patient Withdrawal from the Study

- A patient may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance, or administrative reasons. This is expected to be uncommon.
- A patient who considers withdrawing from the study must be informed by the investigator about modified follow-up options to ensure the collection of endpoints and safety information including new AEs and follow-up on any ongoing AEs and concomitant medications (eg, telephone contact at 30 days (+7 days) after study treatment is discontinued, a contact with a relative or treating physician, or information from medical records).
- At the time of withdrawal from the study, if possible, early study treatment discontinuation procedures should be conducted, as shown in the SoA (Section 1.3). See SoA for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.
  - The patient will discontinue the study treatment and be withdrawn from the study at that time.
- 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.

7.3 Lost to Follow up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and no contact has been established by the time the study is completed (see Section 4.4), such that there is insufficient information to determine the patient's status at that time.

Patients who decline to continue participation in the study, including telephone contact, should be documented as "withdrawal of consent" rather than "lost to follow-up." Investigators should document attempts to re-establish contact with missing patients throughout the study period. If contact with a missing patient is re-established, the patient should not be considered lost to follow-up and evaluations should resume according to the protocol.

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 and ascertain whether or not the patient wishes to and/or should continue in the study.
- Before a patient is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a 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.
- Should the patient continue to be unreachable, he/she will be considered to have withdrawn or been lost to follow-up from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the patient within legal and ethical boundaries for all patients randomised, including those who did not get study treatment. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the patient will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix A.

In order to support key efficacy endpoints of PFS and OS analyses, the survival status of all patients in the full analysis set and the safety analysis set should be re-checked; this includes those patients who withdrew consent or are classified as "lost to follow-up."

- Lost to follow-up – Site personnel should check hospital records and a publicly available death registry (if available), as well as checking with the patient's current physician, to obtain the current survival status (the applicable eCRF modules will be updated).
- In the event that the patient has actively withdrawn consent to the processing of their personal data, the survival status of the patient can be obtained by site personnel from publicly available death registries (if available) where it is possible to do so under applicable local laws.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in the SoA (Section 1.3). Data collection following study analysis until the end of the study is described below.

- Protocol waivers or exemptions are not allowed.

- 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 baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- The maximum amount of blood collected from each patient over the duration of the study, including any extra assessments that may be required, will not exceed 300 mL (over a 1-month). Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

For details on follow-up of patients after discontinuation of study treatment, see Section 7.1.2.

For SAE and AE reporting and laboratory assessment collection after CCI analysis, see Section 8.3.2.

8.1 Efficacy Assessments

8.1.1 Tumour Assessments

Tumour response will be evaluated by the investigator and by BICR (main study only) according to RECIST 1.1. All treatment decisions will be based on on-site assessment of scans. Patients who are determined to have progressed according to RECIST 1.1 criteria by the investigator will have scans centrally reviewed for confirmation of objective disease progression. If disease progression is not confirmed at central review an additional RECIST 1.1 assessment may be requested preferably at the next scheduled RECIST 1.1 visit.

Baseline tumour assessments 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. Baseline assessments should be performed no more than 21 days before randomisation, and ideally should be performed as close as possible to the start of study treatment. The methods of assessment used at baseline should be used at each subsequent follow-up assessment.

Tumour assessment will be conducted every 8 weeks (±1 week) after the start of treatment (Cycle 1 Day 1) up to 18 months, then every 12 weeks (±1 week) until objective disease progression as per RECIST 1.1, irrespective of treatment decisions. In the event of treatment interruptions or delays, tumour assessments should proceed to schedule relative to Cycle 1 Day 1. Tumour assessments (RECIST 1.1) are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression.

Any other sites at which new disease is suspected should also be appropriately imaged. If an unscheduled assessment is performed (eg, to investigate clinical signs and symptoms of progression) and the patient has not progressed, every attempt should be made to perform subsequent assessments at the scheduled visits whilst the patient remains on study treatment.

Digital colour photographs documenting measurable lesions including a ruler to estimate the size of the lesion, should be obtained if the cutaneous lesion is included as part of the non-target lesions for disease assessment according to RECIST 1.1. Copies of the photograph should be forwarded to the central imaging vendor for potential retrospective analysis. The timing for capturing cutaneous lesion photographs should follow the same schedule as the imaging scans.

Clinically stable patients will continue on study treatment following RECIST 1.1 progression after a favourable benefit-risk by the investigator and the Study Physician. Patients who continue treatment beyond radiographic disease progression will be closely monitored. If the follow-up scans do not confirm disease progression per RECIST 1.1, the patient may continue on study treatment.

Categorisation of objective tumour response assessment will be based on the RECIST 1.1 guidelines for response: CR, PR, stable disease, disease progression, and not evaluable.

The RECIST 1.1 guidelines for measurable, non-measurable, TLs and NTLs and the objective tumour response criteria are presented in Appendix G of this protocol.

8.1.1.1 Investigator's Assessment of Tumour Response Per RECIST 1.1

Tumour response will be assessed by the investigators per RECIST 1.1 (Eisenhauer et al, 2009). Guidelines for the evaluation of measurable, non-measurable, TLs, and NTLs and the objective tumour response per RECIST 1.1 are presented in Appendix G.

From the investigator's review of the imaging scans (and photographs if required), the evaluation of TLs, NTLs and new lesions will be used to determine the overall visit response for each patient. Overall visit responses for each visit will then be used to determine if and when a patient has progressed in accordance with RECIST and their best objective response to study treatment.

8.1.1.2 Blinded Independent Central Review of Tumour Assessments

Coded copies of all imaging assessments (regardless of modality and including unscheduled visit scans) will be collected on an ongoing basis and sent to an AstraZeneca appointed iCRO for quality control, storage, and for BICR. Guidelines for image acquisition, de-identification, storage of digital copies at the investigative site (as source documents), and transfer to the iCRO will be provided in the imaging acquisition guideline handling document. Digital copies of all original scans should be stored at the investigator site as source documents. Electronic image transfer from the sites to the iCRO is strongly encouraged. A BICR of images will be performed at the discretion of AstraZeneca. Results of this independent review will not be communicated to investigators and results of the investigative tumour assessments will not be shared with the central reviewers. Management of the patients will be based solely upon the results of the RECIST assessment conducted by the investigator.

The imaging scans will be reviewed by 2 independent radiologists using RECIST 1.1 and will be adjudicated, if required (ie, 2 reviewers will review the scans and, in case of a disagreement, adjudication is performed by a separate reviewer). The independent reviewers will be blinded to study treatment.

The BICR will be conducted on an ongoing basis throughout the study. Where possible scans will be batched, and an in-patient series of assessments read together.

For each patient, the BICR will define the overall visit response (ie, the response obtained overall at each visit by assessing TLs, NTLs, and new lesions) and no programmatic derivation of overall visit response is necessary.

Further details of the BICR will be documented in the BICR Charter.

For the biopsy sub-study, all CT/MRI scans and all imaging assessments performed for RECIST 1.1 tumour assessment will be reviewed at site. Duplicates must be available at the site in readiness to be sent for retrospective independent central RECIST 1.1 review, if deemed appropriate.

8.1.1.3 Screening Assessments

All eligible patients must have confirmed progression during treatment with a PD-(L)1 inhibitor +/- a CTLA-4 inhibitor (eg, nivolumab, pembrolizumab, or atezolizumab, or the combination of nivolumab and ipilimumab) prior to enrolment. Confirmed progression is defined as radiologic progression confirmed by a second scan at 4 to 12 weeks after the initial scan showing disease progression per RECIST 1.1 or, a single scan showing radiological progression accompanied by correlative symptoms suggestive to disease progression.

As part of medical history, copies of the radiological scan reports stating progression will be collected and the investigator asked to confirm whether the patient had 2 scans showing

radiologic progression or a single scan accompanied by correlative symptoms. In the case of patients who have received intervening treatment prior to study entry, a copy of the scan report showing disease progression per RECIST 1.1 prior to study entry will be collected.

8.1.2 Survival follow-up

After discontinuation of study treatment, the survival status of the patients will continue to be collected 8-weekly, reducing to 12-weekly after 18 months, via phone.

Other anti-cancer therapies will be collected 8-weekly, reducing to 12-weekly after 18 months.

8.1.3 Clinical Outcome Assessments

A COA is any assessment that may be influenced by human choices, judgment, or motivation and may support either direct or indirect evidence of treatment benefit.

8.1.3.1 Patient Reported Outcomes

Patient-reported outcome (PRO) assessment is one type of COA and is a general term referring to all outcomes and symptoms that are directly reported by the patient. Patient-reported outcomes have become important in evaluating the efficacy and tolerability of study treatments in clinical studies and will aid in understanding of the benefit/risk evaluation (Kluetz et al 2018).

CCI [redacted]

The PRO measures will be self-administered by patients using an electronic device, at the timepoints indicated in the SoA (Section 1.3). The PRO measures will be provided in the language of the country in which they will be administered.

Each centre must allocate the responsibility for the administration of the questionnaires to a specific individual (eg, a research nurse, study coordinator) and, if possible, assign a back-up to cover absence.

A web back-up may be available to answer the questionnaires if there are technical problems with the device.

Approximately 5 minutes are required on most weeks for patients to complete the questionnaires, and, once a month it will take about 15 minutes to answer the questions.

The below instructions should be followed:

- The research nurse or appointed site staff must explain to the patient the value and importance of completing PRO questionnaires, so they are motivated to comply with questionnaire completion. The patient should be informed that these questions are being asked to find out directly from them how they feel.
- It is vital that the ePRO reporting is initiated at the baseline visit (Cycle 1, Day 1), as specified in the study plan to capture the effect of study treatment. The electronic device must be charged and fully functional at the beginning of the baseline visit to ensure that the PROs can be completed at the start of the visit.
- The patient should bring the ePRO device to each site visit so the research nurse or appointed site staff can check if there are available PRO questionnaires to be completed and that the device is functioning properly.
- PRO questionnaires completed at sites must be completed prior to study treatment administration and ideally before any discussions of health status, to avoid biasing the patient's responses to the questions. As feasible, site staff should also ensure PRO questionnaires are completed prior to other study procedures such as collection of laboratory samples, to further minimise bias.
- On completion of the questionnaire at the site, the device should be handed back to the research nurse or appointed staff nurse, who should check that all questionnaires were completed.
- PRO questionnaires should be completed by the patient in a quiet and private location. The patient should be given the time they need to complete the questionnaires at their own speed.
- The research nurse or appointed site staff should stress that the information is not routinely shared with study staff. Therefore, if the patient has any medical problems, they should discuss them with the doctor or research nurse separately from the PRO assessment.
- The research nurse or appointed site staff must train the patient on how to use the ePRO device, using the materials and training provided by the ePRO vendor.
- The research nurse or appointed site staff must provide guidance on whom to call if there are problems with the device when the patient is completing the ePRO at home.
- All PRO questionnaires must be completed using the ePRO device; paper questionnaires are not allowed in this study. If technical or other device-related issues prohibit completion on the device, an appropriate back-up option may be considered with prior approval from AstraZeneca.
- The research nurse or appointed site staff must remind the patient that there are no right or wrong answers and avoid introducing bias by not clarifying questions for the patient. If

the patient is uncertain about the meaning of a question, the site staff should ask the patient to answer based on what they think the item means.

- The patient should not receive help from relatives, friends, or clinic staff in choosing answers on the PRO questionnaires. The responses are the patient's alone.
- Patients should be reminded to bring visual aids (eg, glasses or contact lenses) for reading to the initial clinic visit. If a patient uses visual aids for reading and does not have them when attending the clinic, the patient will be exempted from completing the PRO questionnaires at that clinic visit but should be asked to complete them at home.
- Site staff must not read or complete the PRO questionnaires on behalf of the patient. If the patient is unable to read the questionnaire (eg, is blind, illiterate or not fluent in the available language), the patient is exempted from completing PRO questionnaires but may still participate in the study. If the patient cannot complete the PRO questionnaires due to reasons other than being blind, illiterate, or fluent in language, the AstraZeneca study team must be contacted to determine if they can be exempted. Patient exempted in this regard should be flagged appropriately by the site staff in the source documents and eCRF.
- Questions must not be translated from an available language in the device into the language the patient speaks.
- Reminders should be provided to patients, as needed, to ensure compliance with the assessment schedules.
- The research nurse or appointed site staff must monitor compliance since minimising missing data is a key aspect of study success.
- Finally, the research nurse or appointed site staff will review the completion status of questionnaires during site visits, and document the reason(s) why a patient could not complete assessments, in the source documents and in the designated eCRF. If the site receives an email notification regarding the patient's compliance, appropriate action will be taken (eg, discussion with patient to improve compliance, a check in call from the site to ask the patient if they have any difficulties in completing questionnaires on schedule, etc). A solution to enhance/resolve compliance should be discussed with the patient. Discussions and compliance review should be reflected in source documents.

A short description of each questionnaire is provided below and sample questionnaires are included in Appendix I.

8.1.3.1.1 CCI

CCI

8.1.3.1.2 CCI

CCI

CCI .

8.1.3.1.3 CCI

CCI

8.1.3.1.4 CCI

CCI

8.1.3.1.5 CCI

CCI

8.1.3.1.6 CCI

CCI

8.1.3.1.7 CCI

CCI

CCI [redacted]

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1 Physical Examinations

Physical examinations, with weight, will be performed regularly at Day 1 of every cycle, at the end of treatment and during the safety follow-up visits, as indicated in the SoA (Section 1.3). Height will be recorded at screening only.

A complete physical examination will be performed and include assessments 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), urogenital, dermatological, gastrointestinal, endocrine, haematologic/lymphatic, neurological systems, height, and weight. Targeted physical examinations are to be used by the investigator on the basis of clinical observations and symptomatology.

Physical examination, as well as assessment of height and weight, will be performed at timelines as specified in the SoA.

Investigators should pay special attention to clinical signs related to previous serious illnesses, new or worsening abnormalities may qualify as AEs; see Section 8.3.5 for details.

8.2.2 Vital Signs

Vital signs (body temperature, BP, respiratory rate, and heart [pulse] rate) will be performed at timelines as specified in the SoA. Any changes in vital signs should be recorded as an AE if applicable.

For patients taking ceralasertib monotherapy: 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 at least 5 minutes of rest for the patient in a quiet setting without distractions (eg, television, cell phones).

Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded on the eCRF.

Situations in which vital signs results should be reported as AEs are described in Section 8.3.5.

For patients receiving ceralasertib plus durvalumab: On the first infusion day (Day 8 of each treatment cycle except for the patients in the ceralasertib monotherapy arm in the main study), patients in the ceralasertib plus durvalumab arm will be monitored and vital signs collected/recorded in the eCRF prior to, during, and after infusion of study treatment as presented in the bulleted list below.

Blood pressure and pulse will be collected from patients in the IO arms before, during, and after each infusion at the following times (based on a 60-minute infusion):

- Prior to the beginning of the 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 (approximately 60 minutes ± 5 minutes)

If the infusion takes longer than 60 minutes, then blood pressure and pulse 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.

Vital signs at subsequent infusions (ceralasertib plus durvalumab)

Blood pressure, pulse and other vital signs should be measured, collected/recorded in eCRF prior to the start of the infusion. Patients should be carefully monitored and blood pressure and other vital signs should be measured during and post infusion as per institution standard and as clinically indicated. Any clinically significant changes in vital signs should be entered onto an unscheduled vital signs CRF page. If no infusion reaction has occurred with the initial infusion, and at the discretion of the investigator, the 1-hour observation period may be shortened or eliminated.

8.2.3 Electrocardiograms

An electrocardiogram will be performed at timepoints as specified in the SoA (Section 1.3).

Resting 12-lead ECG

Triplicate 12-lead ECGs will be done at screening, and single ECG readings will be collected at other visits as clinically indicated. The patient should rest in a semi-supine position for at least 5 minutes before and also during the recording. The ECG machine will automatically calculate the heart rate and measures PR, QRS, QT, and QTcF intervals.

All ECGs should be assessed by the investigator as to whether they are clinically significantly abnormal. Any clinically significant abnormalities detected including a QTcF value > 470 ms require triplicate ECG results. For triplicate ECGs, 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 (5 to 15 minutes window period).

8.2.4 Eastern Cooperative Oncology Group Performance Status

Performance status will be assessed at the visits indicated in the SoA, according to ECOG criteria as follows:

Table 13 Eastern Cooperative Oncology Group Performance Status

Grade	Eastern Cooperative Oncology Group
0	Fully active, able to carry out all pre-disease activities without restrictions
1	Restricted in 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 self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled, cannot carry out self-care, totally confined to bed or chair
5	Dead

Any significant change from baseline or screening in the ECOG performance status must be reported as an AE.

8.2.5 Clinical Safety Laboratory Assessments

Blood and urine samples for determination of clinical chemistry, haematology, coagulation, and urinalysis will be taken at the visits indicated in the SoA (Section 1.3).

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.

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

Other safety laboratory tests include assessment for pregnancy (serum at screening or urine at other time points), HBsAg, HCV antibodies, and HIV antibodies. Pregnancy tests may be performed at the site using a licensed test (urine or serum pregnancy test). Women of childbearing potential are required to have a pregnancy test on Day 1 of every cycle and then as clinically indicated for studies with no suspected teratogenicity/foetotoxicity. Pregnancy test may occur on Day 1, but results must be available and reviewed by the treating physician or investigator prior to commencing study treatment. Abnormal clinically significant laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).

The following laboratory variables will be measured:

Table 14 Laboratory Safety Variables

Haematology/Haemostasis (whole blood)	**Clinical chemistry (serum or plasma)**
Hb	Albumin
Leukocyte count (total white cell count) [a]	ALP[c]
Haematocrit	ALT[c]
Red blood cell count	AST[c]
Leukocyte differential count (absolute count)	Amylase[d]
Neutrophils[a]	Bicarbonate[b]
Lymphocytes[a]	Calcium, total or calcium corrected (for albumin)
Monocytes	Chloride[b]
Basophils	Conjugated bilirubin[c]
Eosinophils	Creatinine and CrCL[b]
Platelet count	C-reactive protein
	Gamma-glutamyl transferase
Coagulation parameters	Glucose (random)
PTT and INR[b]	Lactate dehydrogenase
Urinalysis (dipstick)	Lipase[d]
Glucose	Magnesium[b]
Protein	Phosphate
Blood	Potassium

Table 14 Laboratory Safety Variables

Colour and appearance	Protein, total
pH and specific gravity	Sodium
Bilirubin	TBL[c]
Ketones	TSH
	T3 free (reflex)[e]
Virology (serum): HBsAg, HCV and HIV antibodies [f]	T4 free (reflex)[e]
Pregnancy β-hCG in serum (pre-/screening) or urine (all other visits); only in WOCBP	Unconjugated bilirubin
	Urea nitrogen/blood urea nitrogen, depending on local practice

[a] Can be recorded as absolute counts or as percentages. Total white cell count therefore has to be provided.
[b] Bicarbonate (where available), chloride, creatinine clearance, INR, magnesium and PTT testing are to be performed at baseline, on Day 1 (unless all screening laboratory clinical chemistry and haematology assessments are performed within 3 days prior to Day 1), and if clinically indicated. Creatinine clearance to be calculated using Cockcroft and Gault equation (Cockcroft and Gault 1976).
[c] 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.
[d] It is preferable that both amylase and lipase parameters are assessed. For sites where only 1 of these parameters is routinely measured, either lipase or amylase is acceptable.
[e] Free T3 or free T4 will only be measured if TSH is abnormal or if there is a clinical suspicion of an AE related to the endocrine system.
[f] If patient is HCV-Ag positive, then he/she should be checked for HCV RNA.

NB. In case a patient shows an AST **or** ALT ≥ 3×ULN together with total bilirubin ≥ 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.

AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CK = creatinine kinase; CrCL = creatinine clearance; HB = haemoglobin; INR = international normalised ratio; aPTT = activated partial thromboplastin time T3 = triiodothyronine; T4 = thyroxine; TBL = total bilirubin; TSH = thyroid-stimulating hormone; ULN=upper limit of normal.

Additionally, a serum (screening) or urine (other time points) sample will be collected for pregnancy testing from all women of childbearing potential at the visits indicated in the SoA (Section 1.3).

The investigator should assess the available results with regard to clinically relevant abnormalities in documentation. Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the eCRF. Situations in which laboratory safety results should be reported as AEs are described in Section 8.3.5.

All patients with Grade 3 or 4 laboratory values at the time of completion or discontinuation from study treatment must be followed and have further tests performed until the laboratory values have returned to Grade 1 or 2, unless these values are not likely to improve because of the underlying disease.

8.2.6 Other Safety Assessments

8.2.6.1 Echocardiogram/Multigated Acquisition Scan

An echocardiogram or MUGA scan to assess LVEF will be performed at the visits as shown in SoA (Table 1, Table 2, and Table 3). The modality of the cardiac function assessments must be consistent for a given patient (ie, if echocardiogram is used for the screening assessment for a given patient, then echocardiogram should also be used for subsequent scans for that patient). The patient should also be examined using the same machine and operator whenever possible, and quantitative measurements should be taken (ie, accurate to 1% and not estimated to 5%).

If a patient has had an echocardiogram or MUGA performed within 4 weeks prior to treatment discontinuation, the discontinuation visit echocardiogram/MUGA scan is not required unless clinically indicated. If a patient has any clinically significant decrease in LVEF (greater than 10 percentage points to below 50%), there should be follow-up within 4 weeks until resolution.

Situations in which echocardiogram or MUGA results should be reported as AEs are described in Section 8.3.5.

8.2.6.2 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 the Annex document to this CSP) will be applied. The results of the full diagnostic workup (including high-resolution CT, 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 high-resolution CT 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 (see the Annex document to this CSP) should be followed.

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 (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 that are related to disease progression.
    - Additional clinical chemistry: C-reactive protein and LDH.

8.3 Adverse Events and Serious 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.

Adverse events will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorised representative). For country-specific requirements for Germany see Appendix K 1.3.

The investigator and any designees are responsible for detecting, documenting, recording and reporting events that meet the definition of an AE.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse events and SAEs will be collected from time of signature of ICF, throughout the treatment period and including the safety follow-up period (30 days after last dose of study treatment for ceralasertib monotherapy or 90 days after last dose of study treatment for ceralasertib and durvalumab combination).

If the investigator becomes aware of an SAE with a suspected causal relationship to the study treatment that occurs after the end of the clinical study in a patient treated by him or her, the investigator shall, without undue delay, report the SAE to the sponsor as described in Section 8.3.12.

For patients continuing in the PTAP, AEs and SAEs will be recorded by the treating physician from the time the participant signs informed consent and will continue throughout the program until the end of the PTAP or until consent has been withdrawn. Collection and reporting of AEs and SAEs after the final DCO is described in Section 8.3.11.

8.3.2 Follow-up of AEs and SAEs

Any AEs that are unresolved at the patient's last visit in the study are followed up by the investigator for as long as medically indicated (this may be beyond the 90 days after the last

dose of durvalumab), 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.

Adverse event variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date and time when the AE started and stopped
- Maximum intensity or changes in intensity
- CTCAE grade (version 5.0)
- Whether the AE is serious or not (Appendix B)
- Whether the AE is an AESI or not (Section 8.3.10)
- Investigator causality rating against the study treatment(s) (yes or no)
- Action taken with regard to study treatment(s)
- AE caused patient's withdrawal from study (yes or 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

The grading scales found in the National Cancer Institute CTCAE Version 5.0 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).

8.3.3 Causality Collection

The investigator should assess causal relationship between study treatment 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 treatment?'

For SAEs, causal relationship should 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 protocol.

8.3.4 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the patient or care provider or reported in response to the open question from the study site staff: 'Have you/the patient 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.

8.3.5 Adverse Events Based on Examinations and Tests

The results from the protocol mandated laboratory tests, vital signs, physical examinations, ECGs, and echocardiograms/MUGA scans will be summarised in the CSR.

Deterioration as compared to baseline in protocol-mandated laboratory values and vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria, are the reason for discontinuation of treatment with the study treatment 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 study treatment interruption).

If deterioration in a laboratory value/vital sign/physical examination/ECG/echocardiogram/MUGA is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign/physical examination/ECG/echocardiogram/MUGA 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 per RECIST 1.1, 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 baseline assessment will be reported as an AE unless unequivocally related to the disease under study.

8.3.6 Hy's Law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3 × ULN together with total bilirubin ≥ 2 × ULN may need to be reported as SAEs. Please refer to Appendix E for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

8.3.7 Disease Progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the study treatment is being evaluated. 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 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. If the disease progression worsens in terms of time-course or severity compared to what would normally be expected for that patient, or if the investigator considers that there was a causal relationship between treatment with the study medication(s) or protocol procedures and the disease progression, the event must be reported as an SAE/SUSAR.

8.3.8 New Cancers

The development of a new cancer should be regarded as an AE and will generally meet at least one of the serious criteria. New primary cancers are those that are not the primary reason for the administration of study treatment and are identified after the patient's inclusion in this study. They do not include metastases of the original cancer.

8.3.9 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 treatment, 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 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 the main and contributory causes of death.
- Deaths with an unknown cause should always be reported as an SAE and documented in the Statement of Death page in the eCRF, but every effort should be made to determine a cause of death. 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 time frames.

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

8.3.10 Adverse Events of Special Interest

Adverse events of special interests are events of scientific and medical interest specific to the further understanding of durvalumab and ceralasertib safety profile and require close monitoring and rapid communication by the investigators to AstraZeneca. An AESI can be serious or non-serious. All AESIs will be recorded in the eCRF. Serious AESIs will be recorded and reported as per Section 8.3.12.

AESIs for 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. An immune-mediated AE is defined as an AESI that is associated with drug exposure and is consistent with an immune-mediated MoA and where there is no clear alternate aetiology.

If the investigator has any questions in regard to an event being an immune-mediated AE, the investigator should promptly contact the AstraZeneca clinical lead.

Adverse events of special interest/immune-mediated AE observed with anti-PD-(L)1/PD-1 agents such as durvalumab include pneumonitis, hepatitis, diarrhoea/colitis, intestinal perforation, endocrinopathies (hypo- and hyperthyroidism, adrenal insufficiency, hypophysitis/hypopituitarism and Type 1 diabetes mellitus), nephritis, rash/dermatitis, myocarditis, myositis/polymyositis, pancreatitis and rare/less frequent events (including, but

not limited to haematological events, neuromuscular toxicities [such as myasthenia gravis and Guillain-Barré syndrome], non-infectious encephalitis, non-infectious meningitis, pericarditis, rheumatological events, sarcoidosis, skin events, uveitis [and other events involving the eye] and vasculitis).

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

More detailed guidelines for their evaluation and treatment are described in detail in the Dose Modification and Toxicity Management Guidelines (see the Annex document to this CSP). These guidelines have been prepared by the sponsor to assist the investigator in the exercise of his/her clinical judgement in treating these types of toxicities. These guidelines apply to AEs considered causally related to the study treatment/study regimen by the reporting investigator.

AESIs for ceralasertib

At present there are no AESIs defined for ceralasertib.

8.3.11 Safety Data to be Collected Following the Final Data Cut Off of the Study

See Section 6.7 for treatment after the final DCO and patient management.

For patients continuing to receive ceralasertib or ceralasertib plus durvalumab after the final DCO in the PTAP, no data collection is required except for reporting of non-serious AEs, SAEs, and special situations (ie, pregnancy, overdoses, medication error, and drug abuse and misuse) until the end of post-trial access or until consent has been withdrawn. All data after the final DCO and database closure will be recorded in the patient notes but will not be reported for the purposes of this study except for the safety data mentioned above.

All SAEs that occur in patients still receiving ceralasertib or ceralasertib plus durvalumab in the PTAP must be reported as detailed in Section 8.3.12.

After study completion, when EDC is closed and if an AE/SAE needs to be reported, paper AE/SAE form should be used.

8.3.12 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 during the study conduct.

After study completion, when EDC is closed and SAE needs to be reported, paper SAE form should be used.

If any SAE occurs in the course of the study, then investigators or other site personnel must inform the appropriate AstraZeneca representatives within 1 day ie, immediately but **no later than 24 hours** of when he or 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 **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 AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will 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 or she becomes aware of it.

Once the investigators or other site personnel indicate an AE is serious in the 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 via secure method to the appropriate AstraZeneca representative. Investigators or other site personnel send relevant paper CRF modules by fax to the designated AstraZeneca representative.

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

When the EDC is temporarily not accessible, the AstraZeneca Study Representative should confirm that the investigator/site personnel enter the SAE in the AstraZeneca EDC when access resumes.

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

For regulatory reporting requirements for SAEs, see Appendix A 1.

The reference document for definition of expectedness/listedness is the IB for the AstraZeneca IMPs.

8.3.13 Pregnancy

All pregnancies, including pregnancy in the partner of male patients, and outcomes of pregnancy, with conception dates following the first date of study treatment, should be reported to AstraZeneca.

8.3.13.1 Maternal Exposure

Women of childbearing potential are allowed to be included in this study. Should a pregnancy occur, the study treatment should be discontinued immediately, and the pregnancy reported to AstraZeneca.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study treatment under study may have interfered with the effectiveness of a contraceptive medication. All pregnancies should be collected and provided to the AstraZeneca Data Entry Site (DES) via PREGREP module in the eCRF. If an AE/SAE is associated with the pregnancy, AE/SAE eCRF modules should also be completed and sent to AstraZeneca DES. 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 anomaly/birth defect) should be followed up and documented even if the patient was discontinued from the study. The paper based PREGOUT form should be used to report the outcome of the pregnancy.

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 or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for SAEs (see Section 8.3.8) and **within 30 days** for all other pregnancies.

The same timelines apply when outcome information is available.

8.3.13.2 Paternal Exposure

Non-sterilised male patients who intend to be sexually active with a female partner of childbearing potential should refrain from fathering a child or donating or banking sperm for 6 months after the last dose of study treatment.

Pregnancy in a patient's partner(s) is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital anomaly), occurring from the date of the first dose until 90 days after the last dose and as indicated by previous studies (preclinical and clinical) should, if possible, be followed up and documented in the medical record and provided to the AstraZeneca Patients Safety data entry site. Consent from the partner must be obtained before the information is collected and reported to AstraZeneca via the Pregnancy Report Form. For country-specific requirements for Belgium and France see Appendices K 1.1 and K 1.2, respectively.

Where the report of pregnancy in a patient's partner is received, prior to obtaining information about the pregnancy, the investigator must obtain the consent of the patient's partner. The local study team should adopt the Master Pregnant Partner Form in line with local procedures and submit it to the relevant Regulatory Authority/IRBs/IECs prior to use.

8.3.14 Medication Error, Drug Abuse, and Drug Misuse

8.3.14.1 Timelines

Medication error, Drug Abuse and Drug Misuse alone are not AE/SAE. All Medication Errors/Drug Abuse/Drug Misuse are to be collected for IMPs and provided to AstraZeneca DES via the respective Medication Error eCRF module or Drug Abuse/Drug Misuse paper CRF forms. If an AE/SAE is associated with the Medication Error/Drug Abuse/Drug Misuse, the AE/SAE eCRF modules should also be completed and sent to AstraZeneca DES.

If an event of medication error, drug abuse, or drug misuse occurs during 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 they become 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 event of medication error, drug abuse, or misuse (see Section 8.3.12) and **within 30 days** for all other events.

8.3.14.2 Medication Error

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

The definition of a medication error can be found in Appendix B 4.

8.3.14.3 Drug Abuse

Drug abuse is the persistent or sporadic **intentional**, non-therapeutic excessive use of IMP for a perceived reward or desired non-therapeutic effect.

The full definition and examples of drug abuse can be found in Appendix B 4.

8.3.14.4 Drug Misuse

Drug misuse is the **intentional** and inappropriate use (by a study patient) of IMP for medicinal purposes outside of the authorised product information, or for unauthorised IMPs, 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 4.

8.4 Overdose

For this study, any dose of study treatment greater than 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 ceralasertib, and possible symptoms of overdose are not established. This may include a higher dose of study treatment or study treatment taken at the correct dose but for longer duration.

Overdose alone is not an AE/SAE. All overdoses are collected for IMPs and provided to AstraZeneca DES:

- 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 treatment occurs in the course of the study, the investigator or other site personnel inform appropriate AstraZeneca representatives immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for overdoses associated with an SAE (see Section 8.3.12) and **within 30 days** for all other overdoses.

8.5 Human Biological Samples

Instructions for the collection, storage, and shipping of biological samples will be provided in the study specific Laboratory Manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality.

Samples will be stored for a maximum of 15 years from the end of the study (last patient last visit) in line with consent and local requirements, after which they will be destroyed/repatriated.

- PK samples will be disposed of after the Bioanalytical Report finalisation or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless consented for future analyses.

  - Pharmacokinetic samples may be disposed of or anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled pharmacokinetic samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.
- Remaining sample aliquots will be retained at AstraZeneca or its designee for a maximum of 15 years from the end of the study (last patient last visit). Additional use includes but is not limited to further characterisation of any ADAs, confirmation and/or requalification of the assay as well as additional assay development work. The results from future analysis will not be reported in the CSR.

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

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

Biological samples (eg, archival tumour samples, on-study tumour samples, and blood) will be collected as detailed in the Laboratory Manual in order to carry out biomarker analysis to assess correlations with disease activity, effects of study drug, clinical outcomes and toxicity. The tumour specimens should be of sufficient quality and quantity to allow for next generation sequencing and other analyses to be carried out (see the Laboratory Manual).

The biomarker data may also 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.

For further details on Handling of Human Biological Samples see Appendix C.

8.5.1 Pharmacokinetics

- Venous blood samples for determination of concentrations of study treatment in plasma or serum will be taken at the times specified in the SoA (Section 1.3). The date and time of collection of each sample will be recorded.
- Samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor, eg, for safety reasons. The timing of sampling may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak or trough matrix concentrations) to ensure appropriate monitoring. The total volume of blood taken from each patient will not exceed that presented in Section 8.
- Plasma or serum blood samples will be used to analyse the PK of the study treatment. Samples collected for analyses of study treatment concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

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

8.5.1.1 Determination of Drug Concentration

Samples for determination of study treatment concentration in plasma or serum will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation, if performed, will be reported in a separate Bioanalytical Report.

8.5.2 Immunogenicity Assessments

Blood samples for determination of ADA in serum/plasma will be assayed by bioanalytical test sites operated by or on behalf of the sponsor, using an appropriately validated bioanalytical method. Full details of the methods used will be described in a separate report.

ADA samples may also be further tested for characterisation of the ADA response.

Samples will be collected to evaluate immunogenicity to durvalumab as specified in the SoA. Evaluations will be performed using validated immunoassays. Tiered analyses will be performed to include screening, confirmatory, and titer assay components. Blood samples (~3.5 mL) will be collected at screening, then pre-dose on Day 1 of Cycles 1, 2, 3, and 4, then every 4 cycles, end of treatment, and 30 days after last dose for ceralasertib monotherapy and 30 days, 90 days and 6 months after last dose for ceralasertib and durvalumab combination.

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

8.5.3 Pharmacodynamics

8.5.3.1 Collection of Samples

Blood and urine samples are mandatory and will be collected as per the timepoints detailed in the SoA (Section 1.3).

For storage, re-use and destruction of pharmacodynamic samples see Section 8.5 and Appendix C.

8.6 Human Biological Sample Biomarkers

8.6.1 Collection of Mandatory Samples for Biomarker Analysis

By consenting to participate in the main or biopsy sub-study the patient consents to participate in the mandatory research components of the study.

Tumour and blood samples for biomarker research are required and will be collected from all patients in this study as specified in the SoA (Section 1.3). Samples will be tested for primary, secondary and exploratory objectives, to understand potential candidate predictive biomarkers, pharmacodynamics and MoA of ceralasertib and ceralasertib plus durvalumab, early/late biomarkers of response, and potential resistance mechanisms. The samples may also be used for future diagnostic development

All patients (main study and biopsy sub-study) will be required to provide archival tumour samples (Section 8.6.1.1). The main study will require collection of tumour biopsies at screening, if medically feasible (Section 8.6.1.2). Biopsy sub-study will require collection of serial mandatory tumour biopsies.

Any sample material remaining after completion of analyses to fulfil the study objectives may be used to develop methods, assays, prognostics, and/or diagnostic tests related to cancer, disease process, pathways associated with disease state.

For further details on Handling of Human Biological Samples, including storage, re-use and destruction, refer to Section 8.5 and Appendix C.

8.6.1.1 Mandatory Archival Tumour Samples

Archival tumour tissue (FFPE blocks) obtained within 5 years prior to enrolment and associated pathology report(s) should be obtained at screening for all patients enrolled into the study. Archival tumour tissue must have been formalin fixed for 24 to 48 hours immediately after collection and then embedded in paraffin blocks. If FFPE blocks of archival tumour tissue obtained within 5 years prior to enrolment are not available, then unstained slides (a minimum of 20 freshly cut unstained sections, prepared less than 6 months prior to enrolment) from the relevant archival tumour tissue must be available. CCI [redacted]

CCI [redacted]

CCI [redacted]

8.6.1.2 Tumour Biopsies for Main and Biopsy Sub-Study

All patients must consent to the mandatory use of donated biological samples.

Details of the tumour biopsy collection for the main study and biopsy sub-study are mentioned below. The associated pathology report(s) for fresh tumour samples will be required at

screening and requested on-treatment for all patients enrolled into the study (details in the Laboratory Manual). Where clinically feasible, serial biopsies should be taken from the same lesion and when not feasible, serial biopsies should be taken from the same tissue. Biopsies should be completed with a minimum 18-gauge needle. Fine needle aspirates are not acceptable. Biopsies should not be obtained from bone metastasis. If clinically practical, subjects should undergo 4 core biopsies, but a minimum of at least 3 core biopsies are required. The first and third core biopsies will be placed in formalin and processed for FFPE, while the second and fourth core biopsies (4^{th} biopsy, if available) will be immediately frozen in liquid nitrogen and then stored at -80°C.

Details for fresh tumour sample collection, processing, storage, and shipment are provided in the Laboratory Manual. Per institutional practice, image-guided fresh core needle tumour biopsies should be preferentially obtained from tumour tissues that are safely accessible, as determined by the investigator, and are not obtained from sites that require significant risk procedures. For fresh tumour biopsies, the tumour lesion should not be used as a RECIST target lesion, unless this is the only soft tissue lesion. If a RECIST 1.1 target lesion is used for biopsy, the lesion must be ≥ 2 cm in the longest diameter.

Tumour samples will be analysed for a number of biomarkers with potential association to response or resistance to treatment and/or with the MoA of ceralasertib as monotherapy or in combination with durvalumab. Biomarker may include, but not be limited to: mutations or polymorphisms in specific genes; tumour mutational burden; expression of genes or gene signatures; the number, phenotype, and expression profile of immune cells such as T-cells; the expression of one or more proteins; epigenetic or mutational profiles or signatures.

For main study, A fresh tumour biopsy sample will be collected at screening (Days -21 to -1) unless medically (or technically) not feasible. If a biopsy is not feasible, a tumour tissue sample collected within 5 years prior to enrolment must be provided. If a further tissue sample, independent of age, is available in addition to the mandatory pre-treatment sample, then this should also be provided.

For biopsy sub-study, all study patients are required to provide 3 mandatory fresh tumour biopsy samples for testing at:

- Screening (Days -21 to -1)
- On-ceralasertib treatment, Cycle 0 (on Day 7) of ceralasertib monotherapy, and
- Off-ceralasertib treatment, Cycle 0 (between Days 15 to 28).

Any additional tumour tissue (optional) available should also be submitted.

8.6.1.3 Blood Samples for Exploratory Biomarker Assessments

8.6.1.3.1 CCI

CCI

8.6.1.3.2 CCI

CCI

8.6.1.3.3 CCI

CCI

8.6.1.3.4 CCI

CCI

8.6.1.3.5 CCI

CCI

8.6.1.3.6 CCI

CCI

CCI

8.6.1.3.7 CCI

CCI

8.6.2 Collection of Optional Biomarker Samples

CCI

8.6.2.1 Optional Biopsies

CCI

8.6.3 Other Study Related Biomarker Research

CCI

8.6.4 Optional Future Scientific Research

CCI

8.7 CCI

CCI

- CCI
- CCI

CCI

See Appendix D for information regarding the Genomics Initiative genetic sample.

8.8 Health Economics OR Medical Resource Utilization and Health Economics

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

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

No formal statistical hypotheses are being conducted for this study.

9.2 Sample Size Determination

9.2.1 Main Study

Objective response rate is the primary endpoint in this study. The primary analysis will be conducted once all randomised patients have had a minimum of CCI months of follow-up after start of study treatment or have discontinued from the study, whichever occurs first. It is anticipated that the median duration of follow up for DoR will be at least CCI months at this point, however if not, then the primary analysis may be postponed to ensure a minimum of CCI months median duration of follow up. At this primary analysis the CSR will be written.

It is anticipated at least approximately CCI% of all randomised patients will have progressed or died at the time of the primary analysis. However, if this is not the case, a later analysis for PFS may be conducted once approximately CCI% of all randomised patients have progressed or died.

A CCI analysis will be conducted once approximately CCI% of all randomised patients have died, or CCI years from when the last patient starts treatment, whichever is earliest.

Each treatment arm is experimental and thus will be analysed separately for ORR. The study will recruit approximately 100 patients in the ceralasertib and durvalumab combination therapy arm. With 100 patients the expected CCI width of the CCI% CI for ORR will be up to approximately CCI% when the proportion of patients with an objective response is in the range CCI% to CCI%. For example, ORR CCI%, CCI% CI CCI%, CCI%. The study will recruit approximately 50 patients in the ceralasertib monotherapy arm. With 50 patients, the expected CCI width of the CCI% CI for ORR will be up to approximately CCI% when the proportion of patients with an objective response is in the range CCI% to CCI%. For example, ORR CCI%, CCI% CI CCI%, CCI%. The sample size of the ceralasertib monotherapy arm may be expanded up to a total of approximately 100 patients. This would occur in the event an efficacy signal is observed, and subject to a protocol amendment.

There is no standard of care after anti-PD-(L)1 immunotherapy for the intended patient population. Objective response rate for chemotherapy treatment options for patient second line and beyond, post-ipilimumab, are previously reported to be 4% (95% CI 2%, 9%) and 10% (95% CI 5%, 16%). There is no prospective clinical trial data on response rates for chemotherapy specifically in the post CPI-resistant setting. An ORR of CCI% is considered an upper limit of expected response rate for alternative available treatment options for the intended patient population in this study. Per the proposed Phase 2 study design, with 100 evaluable patients in the ceralasertib and durvalumab combination therapy arm, success will be achieved if a minimum ORR of CCI% is observed, for which the CCI% exact CI would be (CCI %, CCI %).

A secondary objective is to compare the ORR between the two treatment arms. With 150 patients (100 patients randomised to ceralasertib and durvalumab combination therapy arm and 50 patients randomised to ceralasertib monotherapy), there will be at least CCI% power at a CCI of CCI to detect a difference in ORR, assuming an ORR for ceralasertib plus durvalumab of CCI% and an ORR for ceralasertib monotherapy of CCI%.

Enrolled	Estimated CCI patients
Randomly assigned	Estimated 150 patients
Evaluable patients	Estimated 150 patients

Note: "Enrolled" means a patient's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential patients who are screened for the purpose of determining eligibility for the study, but are not randomly assigned/assigned in the study, are considered "screen failures", unless otherwise specified by the protocol. For country-specific requirements for Germany see Appendix K 1.3.

9.2.2 Biopsy Sub-Study

Approximately CCI patients are planned to be enrolled such that approximately 30 patients have at least 2 evaluable paired biopsies (at the baseline and off ceralasertib treatment) including at least 15 patients with at least 3 evaluable biopsies (at baseline, on ceralasertib treatment and off ceralasertib treatment).

Sample sizing is based on expected CCIfold increase in CD8+ T-cells infiltration. The CCIfold assumption represents the observed increase in proliferating CD8+ T-cells infiltration in association with Pembrolizumab and Nivolumab or Nivolumab/Ipilimumab efficacy in melanoma (Tumeh et al, 2014; Grasso et al, 2020).

The sample size of 30 evaluable patients is expected to give adequate sample size to assess changes of CD8+ T-cells from baseline. With 30 evaluable patients and a standard deviation

of CCI -scale), the expected CCI % CI for CD8+ T-cells fold change from baseline is presented in the table below for a range of example observed values.

Table 15 Expected CCI % CI for CD8 T-cells Fold Change from Baseline with a Standard Deviation of CCI -scale) and 30 Evaluable Patients

CD8+ T-cells Change from Baseline	C % Confidence Interval
CCI	

The primary analysis for the biopsy sub-study will be conducted once all enrolled patients have had a minimum of CCI months of follow-up after start of study treatment or have discontinued from the study, whichever occurs first. At this primary analysis the CSR for the biopsy sub-study will be written, which may be finalised after the CSR is finalised for the main study. A CCI analysis will be performed either CCI months after the last patient is enrolled, or CCI % of patients have died, whichever is the earlier event.

9.3 Populations for Analyses

The populations for analysis are listed in Table 16.

Table 16 Populations for Analysis

Population/Analysis set	Description	Endpoint/Output
Enrolled analysis set	All patients who sign the ICF.	Disposition
Safety analysis set	All patients receiving at least 1 dose of study treatment. Patients will be summarised according to the treatment received.	Baseline and demography Exposure Safety ORR BOR TTR DoR Tumour size PFS (biopsy sub-study only) OS (biopsy sub-study)

Population/Analysis set	Description	Endpoint/Output
Full analysis set (main study only)	All patients who are randomised in the study. The FAS will be used for all the efficacy analyses including PROs. Treatment groups will be compared on the basis of randomised study treatment, regardless of the treatment actually received. Patients who were randomised but did not subsequently receive study treatment are included in the analysis in the treatment group to which they were randomised.	Baseline and demography (supportive) ORR (for comparative analysis) PFS OS
PK analysis set	All dosed patients with reportable ceralasertib or durvalumab plasma concentrations. Patients will be summarised according to the treatment received.	PK concentrations
PD analysis set	All patients who receive at least 1 dose of study treatment with at least 1 reportable pharmacodynamic measurement.	PD endpoints
Interim response evaluable (main study only)	All dosed patients who have measurable disease at baseline by BICR and who have first dose at least CCI CCI prior to data cut off.	ORR (interim) BOR (interim) TTR (interim) DoR (interim) Tumour size (interim)

9.4 Statistical Analyses

The statistical analysis plan will be finalised within 90 days of first subject in and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1 General Considerations

Statistical analyses will be performed by AstraZeneca or its representatives including CROs. No adjustments for multiplicity are planned.

9.4.2 Efficacy

9.4.2.1 Primary Endpoint(s)

9.4.2.1.1 Calculation or Derivation of Tumour Response Variables

9.4.2.1.1.1 Investigator RECIST 1.1-based assessments:

All RECIST 1.1 assessments, whether scheduled or unscheduled, will be included in the calculations. This is also regardless of whether a patient discontinues study treatment or receives another anti-cancer therapy.

At each visit, patients will be programmatically assigned a RECIST 1.1 visit response of CR, PR, stable disease, disease progression, or not evaluable depending on the status of their disease compared with baseline and previous assessments. Baseline will be assessed within the 21 days prior to randomisation (or first dose of study drug for the biopsy sub-study). The tumour response endpoints (ORR, DoR, BOR, TTR, PFS, and change in tumour size) will then be derived from the scan dates and overall visit responses.

9.4.2.1.1.2 BICR (Main study only):

A BICR of radiological scans will be performed on all patients in the main study to confirm the robustness of the investigator-assessed ORR, DoR, BOR, TTR, PFS, and change in tumour size endpoints.

All images will be collected centrally. The imaging scans will be reviewed by 2 independent radiologists using RECIST 1.1 and will be adjudicated, if required. For each patient, the BICR will define the overall visit response data (CR, PR, stable disease, disease progression, or not evaluable) and the relevant scan dates for each time point (ie, for visits where response or progression is/is not identified). Patients who have RECIST 1.1-defined disease progression on study treatment based on progression of non-target disease, may also require submission of additional scans/images/photographs eg, brain scan or photographs of cutaneous lesions. If a patient has had a tumour assessment that cannot be evaluated, then the patient will be assigned a visit response of not evaluable (unless there is evidence of progression, in which case the response will be assigned as disease progression). Endpoints ORR, DoR, BOR, TTR, and PFS will then be derived from the scan dates and overall visit responses.

The discordance between investigator assessment and BICR evaluation of measurable disease at baseline will be monitored. If the discordance is high (eg, > 5%), eligibility criteria may be amended to require measurable disease by BICR at baseline.

Further details of the BICR will be documented in an Independent Review Charter.

9.4.2.1.2 Objective Response Rate

Determination of ORR by BICR is the primary objective, and as a sensitivity analysis, ORR by investigator recorded assessments will also be evaluated. Objective response rate is defined

as the proportion of patients who have a CR or PR prior to any evidence of progression (as defined by RECIST 1.1) that is confirmed at least 4 weeks later. The primary analysis of objective response rate will be based upon the safety analysis set. A sensitivity analysis will also be provided in the subset of patients in the safety analysis set who also have measurable disease at baseline by BICR. Data obtained from randomisation up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of ORR, regardless of whether the patient withdraws from therapy. Patients who discontinue treatment without a response or progression, receive a subsequent therapy, and then respond will not be included as responders in the ORR.

As primary analysis, ORR will be summarised for each treatment arm non-comparatively with 95% CI (Clopper-Pearson).

As a secondary objective, ORR will be compared between the treatment arms using logistic regression adjusting for PD-(L)1 resistance type and LDH per randomisation stratification as covariates. The results of the analysis will be presented in terms of an odds ratio for study treatments together with associated 95% profile likelihood CI and p-value (based on twice the change in in log-likelihood resulting from the addition of a treatment factor to the model). This comparative analysis will be provided using the full analysis set.

9.4.2.2 Secondary Endpoints

9.4.2.2.1 Duration of Response

Duration of response will be defined as the time from the date of first documented confirmed response until date of documented progression per RECIST 1.1 as assessed by BICR or death due to any cause. Sensitivity analyses will report DoR using investigator-based assessments with programmatic derivation of the visit response. 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.

If a patient does not progress following a response, then their duration of response will use the PFS censoring time.

Descriptive data will be provided for the duration of response in responding patients, by Kaplan-Meier method including the medians, and landmark estimates at 6, 9, 12, 15, and 18 months with corresponding 95% CI.

9.4.2.2.2 Time to Response

Time to response is defined as the time from the date of randomisation (or date of first dose of study treatment, for the biopsy sub-study) until the date of first documented response. The date of first documented response should coincide with that used for the DoR endpoint. Time to response will not be defined for those patients who do not have a documented response.

The TTR will be summarised (ie, number of patients [%] based upon the number of responders for each treatment arm) by the scheduled assessment timepoint that the response was first observed. Additionally, descriptive summary statistics (ie, minimum, maximum, median, Q1 and Q3) will also be presented.

9.4.2.2.3 Progression Free Survival

Progression free survival is defined as the time from the date of randomisation (or date of first dose for the biopsy sub-study) until the date of objective disease progression per RECIST 1.1 as assessed by BICR or death (by any cause in the absence of progression), (ie, date of event or censoring – date of randomisation/the first dose of study treatment + 1). PFS will be analysed using the full analysis set (main study) and the safety analysis set (biopsy sub-study), and will include all patients in the analysis set regardless of whether the patient withdraws from therapy or receives another anti-cancer therapy or clinically progresses prior to RECIST 1.1 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 assessment. However, if the patient progresses or dies immediately after 2 or more consecutive missed visits, the patient will be censored at the time of the latest evaluable RECIST assessment prior to the 2 missed visits (Note: Not evaluable visit is not considered as missed visit). If the patient has no evaluable visits or does not have baseline data, they will be censored at Day 1 unless they die within 2 visits of baseline (16 weeks plus 1 week allowing for a late assessment within the visit window).

The PFS time will always be derived based on scan/assessment dates and not visit dates.

RECIST 1.1 assessments/scans contributing toward a particular visit may be performed on different dates. The following rules will be applied:

- For investigator assessments, the date of progression will be determined based on the earliest RECIST assessment/scan dates of the component that indicates progression.
- For BICR assessments, the date of progression will be determined based on the earliest dates of the component that triggered the progression on the first set of scans that indicates progression for the adjudicated reviewer selecting disease progression per RECIST 1.1, or of either reviewer where both reviewers select disease progression per RECIST 1.1 as a time point response, and there is no adjudication for central review (BICR) data.
- When censoring a patient for PFS, the patient will be censored at the latest scan dates contributing to a particular overall visit assessment.

Analysis methods:
PFS will be analysed for both BICR and investigator recorded assessment.

Kaplan-Meier plots of PFS will be presented by treatment group. Summaries of the number and percentage of patients experiencing a PFS event and the type of event (RECIST 1.1 or death) will be provided along with median PFS for each treatment. The proportion of patients alive and progression free at 3, 6, 9, and 12 months from randomisation will be summarised by treatment group.

PFS will be analysed using a log rank test stratified by the randomisation stratification factors (baseline LDH and IO resistance). The HR together with its 95% CI and p-value will be presented. The HR and CI will be estimated from a stratified Cox proportional hazards model (with ties = Efron), and the CI will be calculated using a profile likelihood approach. The stratification variables will be defined according to data from the IXRS.

Further sensitivity analyses to explore the robustness of the primary PFS endpoint will be documented in the SAP.

9.4.2.2.4 Overall Survival

The OS is defined as the time from the date of randomisation (or date of first dose for the biopsy sub-study) until death due to any cause regardless of whether the patient withdraws from study treatment or receives another anti-cancer therapy. 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.

Note: Survival calls will be made following the date of DCO for the analysis (these contacts should generally occur within 7 days of the DCO). If patients are confirmed to be alive or if the death date is after the DCO date, then these patients will be censored at the date of DCO.

OS will be analysed using the same methodology specified for PFS, but with landmark estimates summarised at 6, 9, 12, and 18 months from randomisation.

9.4.2.2.5 Change in Tumour Size

Percentage change from baseline in TL tumour size is based on the RECIST 1.1 TL measurements as assessed by BICR. Tumour size is the sum of the longest diameters of the TLs. The percentage change from baseline in TL tumour size at post-baseline assessment (Week 16) is obtained for each patients taking the difference between the sum of the TLs at post-baseline assessment and the sum of the TLs at baseline divided by the sum of the TLs at baseline times 100.

Patients who progress before week 16 should have had a tumour assessment performed at the time of progression prior to treatment discontinuation. The tumour size from their latest progression assessment will be used instead of the week 16 assessment for these patients. Best percentage change will also be summarised.

Best percentage change

The absolute change and percentage change from baseline in the sum of tumour size at each visit will be calculated. The best change in tumour size (ie, depth of response) is the largest decrease from baseline or the smallest increase from baseline in the absence of a reduction and will include all assessments prior to the earliest of death in the absence of progression, any evidence of progression, the start of subsequent anti-cancer therapy or the last evaluable RECIST assessment if the patient has not died, progressed or started subsequent anti-cancer therapy.

The percentage change in target lesion tumour size from baseline at 16 weeks, and best percentage change in tumour size will be presented visually for each patient by waterfall and spider plots.

9.4.2.3 Subgroup Analysis

Subgroup analyses will be conducted, estimating primary and secondary endpoints (ORR, PFS, OS) in the following subgroups (but not limited to):

- Resistance to prior IO treatment (primary / early relapse on adjuvant versus acquired)
- Baseline LDH (<= ULN versus > ULN)
- Resistance to prior IO treatment (primary versus early relapse on adjuvant versus acquired)
- Baseline LDH CCI [redacted]
- Sex (male versus female)
- Age at randomisation (< 65 years versus >= 65 years of age)
- Melanoma subtype (cutaneous versus acral versus mucosal)
- Presence of liver metastases (yes vs no)
- Presence of brain metastases (yes vs no)

Other baseline variables may also be assessed if there is clinical justification or an imbalance is observed between the treatment groups. The purpose of the subgroup analyses is to assess the consistency of treatment effect across expected prognostic and/or predictive factors.

The subgroup analyses for the stratification factors will be based on the values entered into the IWRS; all other factors will be based on the values recorded on the eCRF, or from the third-party vendor data.

Additional subgroups of interest and analysis methods will be outlined in the SAP.

9.4.2.4 Exploratory Endpoint(s)

Planned analysis of exploratory endpoints will be detailed in the SAP.

9.4.3 Safety

All safety analyses will be performed on the safety analysis set. Safety and tolerability will be assessed in terms of AEs (including SAEs), deaths, laboratory data, vital signs, and ECOG. These will be collected for all patients. Appropriate summaries of these data will be presented.

In general, the baseline values for statistical analysis is the last non-missing value prior to administration of the first dose of study treatment. Details are described in the SAP.

9.4.3.1 Adverse Events

AEs will be listed individually by patient and treatment group. For patients who undergo a dose modification, all AEs (due to drug or otherwise) will be assigned to the initial dose group.

Medical Dictionary for Regulatory Activities will be used to code AEs. Adverse events will be graded according to the National Cancer Institute CTCAE (Version 5.0). The number of patients in each treatment arm experiencing each AE will be summarised by MedDRA system organ class and preferred term. The number and percentage of patients with AEs in different categories (eg, causally related, CTCAE Grade ≥ 3, etc) will be summarised by treatment arm; events in each category will be further summarised by MedDRA system organ class and preferred term. Serious adverse events will be summarised separately, if a sufficient number occurs.

Adverse event summary tables will include only treatment-emergent AEs. Adverse Events will be defined as treatment-emergent if they onset or worsen (by investigator report of a change in intensity), during the study treatment or safety follow-up period (defined as 30 days after last dose of study treatment) but prior to subsequent cancer therapy. AEs outside this period will only be listed.

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and AEs leading to discontinuation. Based on the expert's judgement, significant AEs of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered OAEs and reported as such in the clinical study report. A similar review of laboratory/vital signs (pulse and blood pressure) will be performed for identification of OAEs. Examples of these could be marked haematological and other laboratory abnormalities, and certain events that lead to treatment (other than those already classified as serious), dose reduction, or significant additional treatment.

9.4.3.2 Other Safety Endpoint(s)

Clinical chemistry, haematology, urinalysis, and vital signs will be listed individually by patient and appropriately summarised. For all laboratory variables that are included in the CTCAE (version 5.0), the CTCAE grade will be calculated.

Details of any death will be listed for all patients.

9.4.4 Other Analyses

Biopsy sub-study: CD8+ T-cells tumour infiltration and other biomarkers measured in tumour and periphery will be summarised descriptively in baseline, ceralasertib on-treatment and ceralasertib off-treatment samples, and longitudinal blood samples. Data will be transformed as appropriate eg, log_2-transformation, and analysed by MMRM with fixed effect for timepoint. An unstructured variance-covariance matrix will be used to accommodate repeated measures within a patient, assuming model convergence otherwise alternatives will be used as detailed in the SAP. The least square means for each timepoint will be presented, together with the difference to baseline visit and 95% confidence interval.

Association of biomarkers to clinical outcomes will be presented visually, eg, boxplots by BOR.

CCI [redacted]

9.5 Interim Analyses

CCI [redacted] analyses of efficacy data will be conducted during the study.

The CCI [redacted] analysis will be once approximately CCI [redacted] patients have been enrolled (approximately CCI [redacted] patients in the ceralasertib and durvalumab combination therapy arm and approximately CCI [redacted] patients in the ceralasertib monotherapy arm) and had the opportunity for approximately CCI [redacted] weeks follow up. The CCI [redacted] weeks follow up enables CCI [redacted] RECIST scans for confirmation of response. The rationale for this approach is to ensure the ORR is not artificially underestimated at an interim analysis eg, if there are patients ongoing treatment with unconfirmed response who are yet to have their confirmatory scan.

The IDMC may recommend to stop recruitment to the ceralasertib plus durvalumab treatment arm if there are CC [redacted] or CCI [redacted] responses out of CCI [redacted] patients, ie, ORR ≤ CCI [redacted]%. This stop rule corresponds to < CCI [redacted]% predictive probability of success should recruitment continue to the end of the study. There is CCI [redacted]% risk to incorrectly stop if the true ORR = CCI [redacted]%.

The IDMC may recommend to stop recruitment to the ceralasertib monotherapy arm if there are CCI responses out of CCI patients ie, ORR=CCI%. The stop rule for the monotherapy arm is more conservative, intended to mitigate risk of harm relative to other treatment options for patients eg, chemotherapy, but otherwise continuing recruitment in order to have adequate precision in the comparison to the ceralasertib plus durvalumab arm to characterise the contribution of components at study end. Should the combination treatment arm be terminated at the interim analysis, the monotherapy arm may also be terminated if there are CCI or CCI responses out of CCI patients, ie, ORR ≤CCI% since in this situation it is unlikely to achieve the target ORR to warrant future development should it continue to the end of the study.

The CCI analysis will be once approximately CCI patients have been enrolled (approximately CCI patients in the ceralasertib and durvalumab combination therapy arm and approximately CCI patients in the ceralasertib monotherapy arm) and had the opportunity for approximately CCI weeks follow up. The CCI weeks follow up enables CCI RECIST scans for confirmation of response and also preliminary characterisation of the durability of response, which is a key secondary endpoint. The IDMC may recommend to stop recruitment to combination treatment arm if there are CCI or fewer responses out of CCI patients, ie, ORR ≤CCI%. The IDMC may recommend to stop recruitment to monotherapy treatment arm if there are CCI or CCI responses out of CCI patients ie, ORR ≤CCI% and the exact CCI CCI% CI for the proportion of patients with non-progressive disease at week CCI is <CCI%.

Should the combination treatment arm be terminated at the interim analysis, the monotherapy arm may also be terminated if there are CCI or fewer responses out of CCI patients, ie, ORR ≤CCI% since in this situation it is unlikely to achieve the target ORR to warrant future development should it continue to the end of the study. In addition, CCI

ORR will be evaluated by BICR at interim analyses. The IDMC will review all available safety and efficacy data at each interim analysis and any recommendation to stop recruitment to a treatment arm will be based on review of the totality of data across the study. Recruitment will not be paused during the conduct of the interim analyses. Full details on the content of safety and efficacy data reviews will be documented in the IDMC charter.

The SAP will describe the planned interim analyses in greater detail.

In addition, the number of patients with primary IO resistance, early relapse on adjuvant therapy or acquired IO resistance will be monitored throughout the study, and enrolment may be capped to any group at any time to ensure a minimum of approximately CCI% of patients with primary and approximately CCI% of patients with secondary resistance.

9.6 Independent Data Monitoring Committee

An IDMC comprised of independent experts will be convened and will meet for a safety review approximately when [redacted] patients in the ceralasertib and durvalumab combination therapy arm and [redacted] patients in the ceralasertib monotherapy arm achieve 1 cycle (4 weeks) worth of data. The IDMC will convene to review the unblinded safety and tolerability data and the unblinded efficacy data from the interim analyses, in order to recommend to the sponsor to continue, amend, or stop the study based on the safety and efficacy findings. The committee will meet approximately every 3 months thereafter. The IDMC would also perform the interim analysis at the timepoints detailed in Section 9.5.

This committee will be composed of a minimum of 3 therapeutic area experts and biostatisticians, who are not employed by the sponsor and are free from conflict of interest. The precise timings of the initial IDMC meeting and subsequent meetings will be specified in the IDMC Charter. The IDMC Charter will be approved prior to the first IDMC Data Review meeting.

Following the reviews, the IDMC will recommend whether the study should continue unchanged, be stopped, or be modified in any way. Once the IDMC has reached a recommendation, a report will be provided to an unblinded review committee at the sponsor. The report will include the recommendation and any potential CSP amendments. The final decision to modify or stop the study will sit with the sponsor. The sponsor or IDMC may call additional meetings if at any time there is a concern about the safety of the study.

Full details of the IDMC procedures, processes, and interim analyses can be found in the IDMC charter.

For details on IDMC, refer to Appendix A 5.

10 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 ICH 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 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), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- 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 SUSARs to investigational medicinal product will be reported to the EudraVigilance database within the required regulatory timelines.

- For all studies except those utilizing medical devices investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
  - 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 a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

Regulatory Reporting Requirements for Serious Breaches of Protocol or GCP

A 'Serious Breach' means any deviation of the approved version of the protocol or Good Clinical Practice (GCP) that is likely to affect the safety, rights of study patients and/or data reliability and robustness to a significant degree in a clinical trial.

All parties (Sponsor, service provider, investigator site staff) involved in the conduct of the clinical trial:

- Are responsible for promptly identifying and documenting any actual or potential serious breach.
- Should have a process in place to ensure that they are able to identify the occurrence of a (actual/potential) serious breach.
- Should report to AstraZeneca (or delegated party) without delay, 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 and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. 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 centre.
- 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.
- Patients must be re-consented 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.

For country-specific requirements for Germany see Appendix K 1.3.

Patients who are rescreened are required to sign a new ICF.

The ICF will contain a separate section that addresses and documents the collection and use of any mandatory and/or optional human biological samples. The investigator or authorised designee will explain to each patient the objectives of the analysis to be done on the samples and any potential future use of the samples and the data obtained from these samples. Patients will be told that they are free to refuse to participate in any optional samples or the future use and may withdraw their consent at any time and for any reason during the retention period.

If a patient's partner becomes pregnant within 90 days after the last dose of durvalumab, 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.

A 4 Data Protection

- Patients will be assigned a unique identifier by Trusted Third Party contracted by the Sponsor or by a Principal Investigator. Any patient records or datasets that are transferred to AstraZeneca will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.
- The patient must be informed that their personal study-related and coded (pseudonymised) data will be used by AstraZeneca in accordance with local data protection law. The purposes of use and the level of disclosure and use of their data (including the legal basis AstraZeneca relies upon processing their data, where required) must also be explained to the patient in the informed consent.

- The patients must be informed that their medical records may be examined by Quality Assurance auditors or other authorised personnel appointed by AstraZeneca, who are independent of the staff involved in the study in accordance with current Quality Assurance Standard Operating Procedures and Quality Assurance Audit Schedule; by appropriate IRB/IEC members; and by inspectors from regulatory authorities.
- The patient must be informed that data will be collected and used to develop the drug/investigational product, get permission to introduce and keep it on the market, monitor its safety and get it reimbursed eg, by governments eg, throughout the drug development programme, which includes related research activities necessary for this drug development programme, including to: understand how the study drug(s) and similar drugs work in the body (eg, evaluate the study drug mode of action, alone or in combination with other study drugs); better understand the studied disease and associated health problems; develop diagnostic tests for the disease; learn from past studies to plan new studies or improve scientific analysis methods; publish research results in scientific journals or use them for educational purposes. AstraZeneca will only collect and use the minimum amount of personal data to support the research and safety monitoring activities within the drug development programme 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 further pseudonymised and/or anonymised.
- Appropriate safeguards will be implemented to protect coded data during and after the study that include:
  - Access to the coded data will be restricted and monitored, and limited to specific individuals subject to confidentiality obligations (including the obligation to not attempt to re-identify individuals/decode the clinical data).
  - The coded data will be protected with security measures to avoid data alteration, loss, and unauthorised accesses and further de-identification techniques may be applied; as well as other high-standard technical security means such as encryption.
  - A data protection impact assessment, where required, will apply to identify and mitigate privacy risks, if any, associated with each scientific research.
  - The coded data will not be shared for direct marketing purposes or other purposes that are not legal duties or are not related to scientific research purposes of the study. In particular, it will not be used to make decisions about future services available to the patient, such as insurance.
- Patients are also protected legally by the following means, if the coded data will be shared with third parties - other companies within the Sponsor group; Service providers;

Research partners, who may be located in countries which do not offer the same level of protection as the patients' country for which the patient will be informed in the ICF:

- Within the Sponsor group, the patients' coded data are protected by BCR. More information about the Sponsor's BCR is provided here: www.astrazenecabindingcorporaterules.com, or by other contractual arrangements as may be required under local law.
- In all other cases, the patients' coded data is protected by contractual arrangements, Codes of Conduct, or certifications that set the rules for personal data protection to those available in the patient's country or other alternatives set forth in the law, as well as any supplementary technical and organisational measures that may results out of conducted transfer impact assessments, where required.

Personal Data Breaches

A 'personal data breach' means a breach of security leading to the accidental or unlawful destruction, loss, alteration, unauthorised disclosure of, or access to, personal data transmitted, stored or otherwise processed.

- In compliance with applicable laws, the Data Controller[1] for the processing activity where the personal data breach occurred (AstraZeneca or respectively the site), will notify the data protection authorities without undue delay within the legal terms provided for such notification and within the prescribed form and content.
- Whilst AstraZeneca has processes in place to deal with personal data breaches it is important that investigators that work with AstraZeneca have controls in place to protect patient data privacy.

The Investigator should have a process in place to ensure that:

- Allow site staff or service providers delegated by the investigator/institution to identify the occurrence of a (potential) personal data breaches.
- Any (potential) personal data breach is promptly reported to AstraZeneca or delegated party, through the contacts (e-mail address or telephone number) provided by AstraZeneca.

[1] The **data controller** determines the **purposes** for which and the **means** by which personal data is processed, as defined by the European Commission

AstraZeneca and the site must demonstrate that they:

- have taken all necessary steps to avoid personal data breaches and
- have undertaken measures to prevent such breaches from occurring in the first place and to mitigate the impact of occurred data breaches (eg, applying encryption, maintaining and keeping systems and IT security measures up-to-date, regular reviews and testing, regular training of employees, and developed security policies and standards).
- where possible, have developed an internal data breach reporting and investigation process and internal protocols with guidance on how to respond swiftly and diligently to the occurrence of a personal data breach.
- where it has not been possible to develop an internal data breach reporting and investigation process, the site follows AstraZeneca's instructions.

Notification of personal Data Breach to patient:

- Notification to patient is done by the site for the data breaches that occurred within the processing activities for which the site is the Data Controller and for data breaches occurred within the processing activities of AstraZeneca as the Data Controller, the notification is done in collaboration with the site and is performed by the site and/or Principal Investigator, acting on behalf of AstraZeneca, so that AstraZeneca has no access to the identifying personal information of the patient. The site and/or Principal Investigator shall conduct the notification by contacting the patient using the information that they gave for communication purposes in clinical research.
- If a personal data breach occurs in a processor's systems, engaged by AstraZeneca, the processor under contractual obligations with AstraZeneca promptly and in due course after discovering the breach notifies AstraZeneca and provides full cooperation with the investigation. In these cases, to the extent AstraZeneca is the Data Controller for the processing activity where the breach occurred, it will be responsible for the notification to data protection authorities and, if applicable, to patient. If the personal data breach needs to be notified to the patient, the notification to patient is done in collaboration with the site and is performed by the site and/or Principal Investigator, acting on behalf of the Sponsor, so that AstraZeneca has no access to the identifying personal information of the patient.
- If a personal data breach involving an AstraZeneca's representative device (ie, Study Monitor laptop), AstraZeneca representative will provide AstraZeneca with all of the information needed for notification of the breach, without disclosing data that allows AstraZeneca directly or indirectly to identify the patient. The notification will be done by AstraZeneca solely with the information provided by the Study Monitor and in no event with access to information that could entail a risk of re-identification of the patient. If the data breach must be notified to the data subjects, the notification will be done directly by

the Study Monitor in collaboration with the site and/or Principal Investigator, acting on behalf of the Sponsor, so that AstraZeneca has no access to the identifying personal information of the patient. The contract between AstraZeneca and the Study Monitor shall expressly specify these conditions.

- The contract between the site and AstraZeneca for performing the clinical research includes the provisions and rules regarding who is responsible for coordinating and directing the actions in relation to the breaches and performing the mandatory notifications to authorities and patients, where applicable.

A 5 Committees Structure

The safety of all AstraZeneca clinical studies is closely monitored on an ongoing 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.

A 6 Dissemination of Clinical Study Data

Study overall results, both technical and written in lay language (Trial Results Summary, also known as Lay Language Summary of overall study results), will be submitted to EU CTIS within a year from global End of Trial Date in all participating countries, to ensure scientific integrity, completeness, robustness and reliability of data published results.

A description of this clinical study will be available on http://astrazenecaclinicaltrials.com and http://www.clinicaltrials.gov and https://euclinicaltrials.eu/ as will the summary of the study results when they are available. The clinical study and/or summary of 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 eCRF 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 eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory authority inspections and provide direct access to source data documents.
- 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 non-compliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan/contracts.

- The sponsor 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 Monitoring Plan/contracts.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organisations).
- Study monitors will perform ongoing source data verification as per the Monitoring Plan(s) to confirm that data entered into the eCRF 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 a minimum of 25 years after study archiving or as required 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 eCRF 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.
- Definition of what constitutes source data can be found in Source Data Agreement. All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study are defined as source documents.

A 9 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of patients.

The first act of recruitment is the first site open and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. 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 patients by the investigator
- Discontinuation of further study treatment development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organisation(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the patient and should assure appropriate patient therapy and/or follow-up.

A 10 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 multicentre 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. Detailed authorship guidelines will be outlined in a separate authorship policy.

Appendix B Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

B 1 Definition of Adverse Events

An adverse event is the development of any untoward medical occurrence (other than progression of the malignancy under evaluation) in a patient or clinical study patient administered a study treatment 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 in-patient 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

Adverse Events (AEs) for **malignant tumours** reported during a study should generally be assessed as **Serious AEs**. If no other seriousness criteria apply, the ‘Important Medical Event’ criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a **non-serious AE**. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfil the attributes for being assessed as serious, although reporting of the progression of the malignant tumour as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalisation, may be assessed as non-serious;

examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

The above instruction applies only when the malignant tumour event in question is a new malignant tumour (ie, it is *not* the tumour for which entry into the study is a criterion and that is being treated by the Investigational Product under study and is not the development of new or progression of existing metastasis to the tumour under study). Malignant tumours that – as part of normal, if rare, progression – undergo transformation (eg, Richter's transformation of B-cell chronic lymphocytic leukaemia into diffuse large B-cell lymphoma) should not be considered a new malignant tumour.

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).

Hospitalisation

Outpatient treatment in an emergency room is not in itself an 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.

Important Medical Event or Medical Treatment

Medical and scientific judgement 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 judgement 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

Intensity Rating Scale:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious 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.

The grading scales found in the revised National Cancer Institute CTCAE, version 5.0, 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). The applicable version of CTCAE should be described clearly.

B 3 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 judgement. With no available facts or arguments to suggest a causal relationship, 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 4 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 treatment 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 IVRS/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 IMP or AstraZeneca NIMP 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 IMP for medicinal purposes outside of the authorised product information, or for unauthorised IMPs, 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

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) and records relevant processing information related to the samples whilst at site.

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 record of receipt of arrival and onward shipment or disposal.

AstraZeneca or delegated representatives 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 AstraZeneca-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca Team during for the remainder of the sample life cycle.

If required, AstraZeneca will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is the sooner.

C 2 Withdrawal of Informed Consent for Donated Biological Samples

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.

If a patient withdraws consent specifically to the subsequent use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research. The patient will be presented with the option to opt out of the subsequent use of the donated samples during the withdrawal process. If the patient decides to opt out, then the donated samples will be disposed of. If the patient withdraws consent without opting out for the subsequent use of the donated samples, then the samples will be used as per protocol.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The investigator:

- Ensures patient's withdrawal of informed consent to the use of donated samples is highlighted immediately to AstraZeneca or delegate.
- Ensures that relevant human biological samples from that patient, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.
- 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 or repatriated as appropriate, and the action is documented and study site notified.

C 3 International Airline Transportation Association 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) (**https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx**) classifies infectious substances into 3 categories: Category A, Category B or Exempt

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. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900.

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, C, D, and E viruses. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN 3373 and IATA 650

Exempt – Substances which do not contain infectious substances or substances which are unlikely to cause disease in humans or animals are not subject to these Regulations unless they meet the criteria for inclusion in another class.

- Clinical study samples will fall into Category B or exempt under IATA regulations
- Clinical study 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

Appendix D CCI

D 1 CCI

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D 2 CCI

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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 Potential Hy's Law (PHL) cases and Hy's Law (HL) cases. 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 potential 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 AE 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 treatment.

The investigator is responsible for recording data pertaining to PHL/HL cases and for reporting SAEs and AEs according to the outcome of the review and assessment in line with standard safety reporting processes.

E 2 Definitions

Potential Hy's Law
Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3 × ULN **together with** Total Bilirubin (TBL) ≥ 2× ULN at any point during the study following the start of study treatment irrespective of an increase in ALP.

Hy's Law
AST or ALT ≥ 3× ULN **together with** TBL ≥ 2× ULN, where no other reason, other than the study treatment, 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 timeframe 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 patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 × ULN
- AST ≥ 3 × ULN
- TBL ≥ 2 × ULN

Local Laboratories Being Used:

The investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify AstraZeneca representative
- Determine whether the patient meets PHL criteria (see Appendix E 2 for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory eCRF

E 4 Follow-up

E 4.1 Potential Hy's Law Criteria Not Met

If the patient does not meet PHL criteria the investigator will:

- Inform the AstraZeneca representative that the patient has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the CSP.

E 4.2 Potential Hy's Law Criteria met

If the patient does meet PHL criteria the investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment (see Appendix E 6)
- 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 PHL; serious criterion "Important medical event" and causality assessment "yes/related" according to CSP process for SAE reporting
- For patients that met PHL criteria prior to starting study treatment, the investigator is not required to submit a PHL SAE unless there is a significant change[#] in the patient's condition
- The study clinical lead contacts the investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up (including any further laboratory testing) and the continuous review of data
- Subsequent to this contact the investigator will:
  - Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
  - Investigate the aetiology of the event and perform diagnostic investigations as discussed with the study clinical lead. This includes deciding whether the tests available in the Hy's law lab kit should be used.
  - Complete the three Liver eCRF Modules as information becomes available

[#]**A 'significant' change** in the patient'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 clinical lead if there is any uncertainty.

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 clinical lead 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 treatment, 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 eCRF
- If the alternative explanation is an AE/SAE: update the previously submitted PHL SAE and AE eCRFs 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 treatment:

- 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 PHL, (report term now 'Hy's Law case') ensuring causality assessment is related to study treatment 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 and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

E 6 Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment

This section is applicable to patients with liver metastases who meet PHL criteria on study treatment, having previously met PHL criteria at a study visit prior to starting study treatment.

At the first on study treatment occurrence of PHL criteria being met the investigator will determine if there has been a **significant change** in the patient's condition[#] compared with the last visit where PHL criteria were met[#]

- If there is no significant change no action is required.
- If there is a significant change, notify the AstraZeneca representative, who will inform the central Study Team, then follow the subsequent process described in Appendix E 4.2

E 7 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 questions:

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 E 4.2 for reporting PHL as an SAE

If **Yes**: Determine if there has been a significant change in the patient'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 E 4.2 for reporting PHL as an SAE

[#] **A 'significant' change** in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) 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 8 Laboratory Tests

The list below represents the standard, comprehensive list of follow-up tests, which are recommended but not mandatory. The list may be modified based on clinical judgement. Any test results need to be recorded.

Hy's Law Lab Kit	
Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR
Viral hepatitis	IgM anti-HAV HbsAg IgM and IgG anti-HBc HCV DNA [a] IgM and IgG anti-HCV HCV RNA [a] 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) [b]
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 [b] Transferrin saturation

CMV = cytomegalovirus; DNA = deoxyribonucleic acid; EBV = Epstein-Barr virus; GGT = gamma glutamyl transferase; HAV = hepatitis A virus; HBc = hepatitis B core antigen; HbsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HEV = hepatitis E virus; HSV = herpes simplex virus; IgG = immuno-globulin G; IgM = immuno -globulin M; INR = international normalised ratio; LDH = lactate dehydrogenase; RNA = ribonucleic acid.

[a] HCV RNA; HCV DNA are only tested when IgG anti-HCV is positive or inconclusive.

[b] CD-transferrin and Transferrin are not available in China. Study teams should amend this list accordingly

E 9 References

Aithal et al, 2011
Aithal et al 2011, Clinical Pharmacology and Therapeutics 89(6):806-815.

FDA Guidance for Industry, July 2009
FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation'. Available from; https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-induced-liver-injury-premarketing-clinical-evaluation

Appendix F Guidelines Regarding Potential Interactions of Ceralasertib with Concomitant Medications

Restrictions regarding drugs affecting CCI metabolism

There are currently no data confirming that there is a pharmacokinetic (PK) interaction between these agents and ceralasertib; a potential interaction is considered on the basis of preclinical and in vitro data only. Ceralasertib is predominantly eliminated via CCI metabolism, therefore CCI may increase or decrease exposure to ceralasertib, respectively. CCI of CCI should not be combined with ceralasertib. In vitro data also suggest that ceralasertib may be metabolised by CCI but a lesser extent, therefore caution should be applied with co-administration of potent inhibitors or inducers of CCI.

These lists are not intended to be exhaustive, and similar restrictions will apply to other agents that are known to modulate CCI activity. Please contact AstraZeneca with any queries you have on this issue. Please refer to full prescribing information for all drugs prior to co-administration with ceralasertib.

Drugs Known to be Inhibitors or Inducers of CCI

Potent CCI inhibitors	Potent CCI inducers
CCI	CCI

a CCI

b CCI

Drugs Known to be Inhibitors and Inducers of CCI

Potent CCI inhibitors	Potent CCI inducers
CCI	CCI

List created using the University of Washington Drug-Drug Interaction Database Jan 2020.

Drugs known to be inhibitors or inducers of CCI and/or CCI, undertake appropriate monitoring if co-administration is necessary

Ceralasertib is a substrate of CCI and CCI. Co-administration of CCI inhibitors/inducers or CCI inhibitors/inducers may affect exposure to ceralasertib therefore it is recommended that these are not co-administered with ceralasertib.

These lists are not intended to be exhaustive, and similar restrictions will apply to other agents that are known to modulate CCI activity or CCI activity. Please contact AstraZeneca with any queries you have on this issue. Please refer to full prescribing information for all drugs prior to co-administration with ceralasertib.

Drugs Known to be Inhibitors or Inducers of CCI

Drugs Known to be Inhibitors of CCI	Drugs Known to be Inducers of CCI
CCI	CCI

Drugs Known to be Inhibitors of CCI	Drugs Known to be Inducers of CCI
CCI [redacted]	

Drugs Known to be Inhibitors of CCI	Drugs Known to be Inducers of CCI
CCI	

List created using the University of Washington Drug-Drug Interaction Database October 2019.

Drugs Known to be Inhibitors or Inducers of CCI

Drugs Known to be Inhibitors of CCI	Drugs Known to Be Inducers of CCI
CCI	CCI

Drugs Known to be Inhibitors of CCI	Drugs Known to Be Inducers of CCI
CCI	

CCI

Drugs known to be substrates of CCI and/or CCI or CCI or CCI, or CCI undertake appropriate monitoring if co-administration is necessary

Ceralasertib is a potential inducer of CCI and a potential inhibitor of CCI. Therefore, caution should be applied with co-administration of drugs that are either completely metabolised by CCI, or that are substrates of CCI and also have a narrow therapeutic index. Investigators should be aware that the exposure of other drugs co-administered with ceralasertib that are metabolised by CCI may be increased due to inhibition, and exposure of other drugs co-administered with ceralasertib that are metabolised by CCI may be reduced due to induction.

Drugs known to be metabolised by CCI

Metabolised by CCI	Metabolised by CCI	Metabolised by CCI	Metabolised by CCI	Metabolised by CCI
CCI	CCI	CCI	CCI	CCI

Metabolised by CCI	Metabolised by CCI	Metabolised by CCI	Metabolised by CCI	Metabolised by CCI
CCI				

Metabolised by CCI	Metabolised by CCI	Metabolised by CCI	Metabolised by CCI	Metabolised by CCI
CCI				

CCI

(NTR) drug listed in the Narrow Therapeutic Index list by CCI in DrugBank

Drugs known to be substrates of CCI, undertake appropriate monitoring if co-administration is necessary

Ceralasertib is also an inhibitor of CCI. Caution should be applied with co-administration of substrates of CCI as ceralasertib may increase their exposure.

These lists are not intended to be exhaustive and appropriate medical judgement is required. Please contact AstraZeneca with any queries you have on this issue. Please refer to full prescribing information for all drugs prior to co-administration with ceralasertib.

Drugs Known to be Substrates of CCI

CCI

* CCI

CCI

Drugs known to be substrates of CCI

CCI

CCI

Appendix G Guidelines for Evaluation of Objective Tumour Response Using RECIST 1.1 (Response Evaluation Criteria in Solid Tumours)

Introduction

This appendix details the implementation of RECIST 1.1 guidelines (Eisenhauer et al, 2009) for the study with regards to investigator assessment of tumour burden including protocol-specific requirements for this study.

Assessment of Disease using RECIST 1.1

Definition of Measurable, Non-measurable, Target and Non-target Lesions

Patients with at least one lesion (measurable and/or non-measurable) that can be accurately assessed at baseline by computerised tomography, MRI or plain X-ray should be included in this study.

Measurability of tumour lesions at baseline

RECIST 1.1 measurable lesions at baseline

A tumour lesion that can be accurately measured at baseline as ≥ 10 mm in the longest diameter for non-nodal lesions or ≥ 15 mm in short axis[2] diameter for lymph node lesions with IV contrast-enhanced CT or MRI and that is suitable for accurate repeated measurements. Please see additional RECIST 1.1 guidance below on measurability of intrahepatic hepatocellular carcinoma lesions and porta hepatis lymph nodes.

Non-measurable lesions at baseline

- Truly non-measurable lesions include the following:
  - Bone lesions (see exception below for soft tissue component).
  - Leptomeningeal disease.
  - Ascites, pleural effusion, or pericardial effusion.
  - Inflammatory breast disease.
  - Lymphangitic involvement of skin or lung.
- All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 mm to < 15 mm short axis diameter at baseline).[3]

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[2] The short axis is defined as the longest in-plane axis perpendicular to the long axis.
[3] Lymph nodes with < 10 mm short axis diameter are considered non-pathological and should not be recorded or followed as NTLs.

- Previously irradiated lesions.
- Brain metastasis.

Special considerations regarding lesion measurability at baseline

- Bone lesions:
  - Bone scan, PET scan, or plain X-ray are not considered adequate imaging techniques to measure bone lesions; however, these techniques can be used to confirm the presence or disappearance of bone lesions.
  - 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 lesions thought to represent 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 over cystic lesions as TLs.

RECIST 1.1 TL selection at baseline

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes collectively considered as a single organ), representative of all lesions involved should be identified as TLs at baseline. TLs should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis diameter 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 that can be measured reproducibly should be selected.

Lymph nodes, in any location (local/regional and distant), are collectively considered as a single organ, with a maximum of 2 lymph nodes as TLs. A bilateral organ (eg, adrenal glands), a segmented organ (eg, liver), or a multilobed organ (eg, lung) is each considered as a single organ.

The site and location of each TL should be documented, as well as the longest axis diameter for non-nodal lesions (or short axis diameter for lymph nodes). All measurements should be recorded in millimetres. At baseline, the sum of the diameters for all TLs will be calculated and reported as the baseline sum of diameters. At follow-up visits, the sum of diameters for all TLs will be calculated and reported as the follow-up sum of diameters.

Special cases for TL assessment at baseline

- For TLs 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 diameter.
- When lymph nodes are coalesced and no longer separable in a conglomerate mass, the vector of the longest diameter should be used to determine the perpendicular vector for the maximal short axis diameter of the coalesced mass. Non-nodal lesions that coalesce should similarly be assessed by the longest axis diameter.
- Tumour lesions selected for newly acquired screening biopsy should not be selected as TLs, unless imaging occurred at least approximately 2 weeks after biopsy, allowing time for healing.
- If the CT/MRI slice thickness used is > 5 mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.
- If a lesion has completely disappeared, the diameter should be recorded as 0 mm. If a lesion appears in the same location on a subsequent scan, it will be recorded as a NL.

RECIST 1.1 NTL selection at baseline

All other lesions, including non-measurable lesions and surplus measurable lesions, not recorded as TLs should be identified as NTLs at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Evaluation of tumour response and progression

RECIST 1.1 TL assessment at follow-up

This section defines the criteria used to determine objective tumour visit response for RECIST 1.1-defined TLs. The imaging modality, location, and scan date of each TL identified previously at baseline should be documented at follow-up visits with the long axis diameter for non-nodal lesions or short axis diameter for lymph node lesions. All measurements should be recorded in millimetres. The sum of the diameters for all TLs at each follow-up visit will be compared with the baseline sum of diameters (for response or SD) or to the smallest prior (nadir) sum of diameters (for progression).

Special cases for TL assessment at follow-up:

- If a lesion has completely disappeared, the diameter should be recorded as 0 mm. If a lesion appears in the same location on a subsequent scan, it will be recorded as an NL.
- If a TL splits into 2 or more parts, the sum of the diameters of those parts should be recorded.
- If 2 or more TLs merge, then the sum of the diameters of the combined lesion should be recorded for 1 of the lesions and 0 mm recorded for the other lesion(s). If the merged TLs are non-nodal lesions, record the long axis diameter of the merged lesion. If pathologic

lymph nodes coalesce and are no longer individually separable within a conglomerate mass, the vector of the longest diameter of the coalesced mass should be used to determine the perpendicular vector for the maximal short axis diameter.

- 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. The choice of "Too large to measure" in the CRF will trigger an overall visit response of PD.
- When a TL has had any intervention (eg, definitive radiotherapy, embolisation, surgery, transarterial chemoembolisation, etc) during the study, the size of the TL should still be provided where possible and the intervention recorded in the RECIST 1.1 CRF for the current imaging visit and all subsequent visits. If a TL has been completely removed (surgery) or disappears, the longest diameter should be recorded as 0 mm.

Table 17 RECIST 1.1 Evaluation of Target Lesions

CR	Disappearance of all TLs since baseline. Any pathological lymph nodes selected as TLs must have a reduction in short axis diameter to < 10 mm.
PR	At least a 30% decrease in the sum of the diameters of TL, taking as reference the baseline sum of diameters.
SD	Neither sufficient decrease in the sum of diameters to qualify for PR nor sufficient increase to qualify for PD.
PD	At least a 20% increase in the sum of diameters of TLs, taking as reference the smallest previous sum of diameters (nadir). This includes the baseline sum if that is the smallest on study. In addition to the relative increase of 20%, the sum must demonstrate an absolute increase of at least 5 mm from nadir.
NE	Only relevant if any of the TLs at follow-up were not assessed or NE (eg, missing anatomy) or had a lesion intervention at this visit. Note: If the sum of diameters meets the PD criteria, PD overrides NE as a TL response.
Not applicable	Only relevant if no TLs present at baseline.

CR, complete response; NE, not evaluable; PD, progression of disease; PR, partial response; SD, stable disease; TL, target lesion.

RECIST 1.1 NTL assessment at follow-up

All other lesions (or sites of disease) not recorded as TLs should be identified as NTLs at baseline. 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.

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 SD or PR in TLs,

the overall tumour burden has increased sufficiently to merit unequivocal progression by NTLs. A modest "increase" in the size of 1 or more NTLs is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PD of target disease will therefore be extremely rare.

Table 18 RECIST 1.1 Evaluation of Non-Target Lesions

CR	Disappearance of all NTLs since baseline. All lymph nodes must be non-pathological in size (< 10 mm short axis).
Non CR/non PD	Persistence of 1 or more NTLs.
PD	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in 1 lesion only or in several lesions. In all cases, the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
NE	Only relevant when 1 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 baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met.
Not applicable	Only relevant if no NTLs present at baseline.

CR, complete response; NE, not evaluable; NTL, non-target lesion; PD, progression of disease; TL, target lesion.

RECIST 1.1 NL identification at follow-up

Details, including the imaging modality, the date of scan, and the location of any NLs will also be recorded in the CRF. The presence of 1 or more NLs is assessed as progression. The finding of a NL 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 NL is equivocal, for example because of its small size, the treatment and tumour assessments should be continued until the previously (pre-existing) NL has been assessed as unequivocal at a follow-up visit, and then the progression date should be declared using the date of the initial scan when the NL first appeared.

A lesion identified at a follow-up assessment in an anatomical location that was not scanned at baseline is considered a NL and will indicate PD.

RECIST 1.1 evaluation of overall visit response at follow-up

Derivation of overall visit response as a result of the combined assessment of TLs, NTLs, and NLs uses the algorithm shown in Table 19.

Most studies should require at least 1 TL at baseline (please see Inclusion Criteria). For these studies, please delete the rows and footer text in green font below. For studies where there is no mandatory requirement to have measurable disease at baseline and therefore it is possible

to have not applicable in TLs at baseline, please retain rows and footer text in green font. For country-specific requirements for Germany see Appendix K 1.3.

Table 19 RECIST 1.1 Overall Visit Response

Target lesions	Non-target lesions	New lesions	Overall visit response
CR	CR	No	CR
CR	NA	No	CR
NA	CR	No	CR
CR	Non CR/Non PD	No	PR
CR	NE	No	PR
PR	Non PD or NE or NA	No	PR
SD	Non PD or NE or NA	No	SD
NA	Non-CR/Non-PD	No	SD (non-CR/non-PD)
NE	Non PD or NE	No	NE
NA	NE	No	NE
NA	NA	No	NED
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Non-CR/Non-PD for overall response if only NTL (no TLs) are present at baseline.

Note: An overall assessment of CR (all other disease disappears/reverts to normal) would be changed to PR if ascites remains present radiologically.

CR, complete response; NA, not applicable (only relevant if there were no TLs at baseline or NTLs at baseline), NE, not evaluable; NED, no evidence of diseases (only relevant if there were neither TLs nor NTLs at baseline); NTL, non-target lesion; PD, progression of disease; PR, partial response; SD, stable disease; TL, target lesion.

The following overall visit responses are possible depending on the extent of tumour disease at baseline:

- For patients with TLs (at baseline): CR, PR, SD, PD, or NE.
- For patients with NTLs only (at baseline): CR, Non-CR/Non-PD, PD, or NE.
- For patients with no disease at baseline: no evidence of disease (available as an option in the eCRF), PD, or NE.

Evaluation of scans subsequent to RECIST 1.1-defined progression

A follow-up scan is requested at least 4 weeks after a RECIST 1.1-defined radiological progression and no longer than the next regularly scheduled imaging visit. The follow-up scans provide additional information to the investigator for patient management and further treatment decisions, and since the published RECIST 1.1 criteria (Eisenhauer et al, 2009) do not provide guidance on how to assess scans acquired after RECIST 1.1-defined PD,

supplemental instructions for investigators on how to evaluate these follow-up scans are provided below. An immediate prior RECIST 1.1-defined radiologic PD would be considered confirmed if *any* of the following criteria are met in the subsequent follow-up scan:

- ≥ 20% increase and at least a 5 mm increase in the sum of diameters of TLs compared with the nadir sum of diameters at 2 consecutive visits, and a further increase of ≥ 5 mm in the sum of diameters at the follow-up scan time point compared with the immediate prior time point.
- Significant progression (worsening) of NTLs at the follow-up scan time point compared with the immediate prior time point.
- Significant progression (worsening) of previously NLs (pre-existing NLs) at the follow-up scan time point compared with the immediate prior time point.
- Additional brand-new unequivocal lesions at the follow-up scan time point.

Methods of Measurement

The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow-up.

The methods to be used for RECIST assessment are summarised in the below table and those excluded for tumour assessments in this study are discussed below, with the rationale provided.

Table 20 Summary of Methods of Assessment

Target Lesions	Non-target Lesions	New Lesions
CT (preferred)	CT (preferred)	CT (preferred)
MRI	MRI	MRI
	Plain X-ray	Plain X-ray
	Chest X-ray	Chest X-ray
		Bone scan (Scintigraphy)
		^{18}F-fluoro-deoxyglucose-PET/CT

CT = computed tomography; PET/CT = positron emission tomography; MRI = magnetic resonance imaging.

For skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion, is required (2 dimensions is acceptable). When lesions can be evaluated by both clinical examination and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Photographs include a close-up view of the index lesion area(s), anatomical location view of the index lesion area(s). Two exposures for each location and lesion will be taken.

CT and MRI

CT with IV contrast is the preferred imaging modality (although MRI with IV contrast is acceptable if CT is contraindicated) to generate reproducible anatomical images for tumour assessments (ie, for measurement of TLs, assessment of NTLs, and identification of NLs). It is essential that the same correct imaging modality, image acquisition parameters (eg, anatomic coverage, imaging sequences, etc), imaging facility, tumour assessor (eg, radiologist), and method of tumour assessment (eg, RECIST 1.1) are used consistently for each patient throughout the study. The use of the same scanner for serial scans is recommended, if possible. It is important to follow the image collection/tumour assessment schedule as closely as possible (refer to the SoA), and this on-study imaging schedule MUST be followed regardless of any delays in dosing or missed imaging visits. If an unscheduled assessment is performed (eg, to investigate clinical signs/symptoms of progression) and the patient has not progressed, every attempt should be made to perform the subsequent scan acquisitions at the next scheduled imaging visit.

Due to its inherent rapid acquisition (seconds), CT is the imaging modality of choice. Body scans should be performed with breath-hold scanning techniques, if possible. Therefore, CT of the chest is recommended over MRI due to significant motion artefacts (eg, heart, major blood vessels, breathing) associated with MRI. MRI has excellent contrast and spatial and temporal resolutions; 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 baseline, and the lesions should be measured/assessed on the same pulse sequence. In general, local oncology diagnostic imaging parameters are applied for scan acquisition. It is beyond the scope of this appendix to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases.

The most critical CT and MRI image acquisition parameters for optimal tumour evaluation are anatomic coverage, contrast administration, slice thickness, and reconstruction interval.

a. Anatomic coverage: Optimal anatomic coverage for most solid tumours is the chest-abdomen (-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 baseline would be considered as a NL representing PD, careful consideration should be given to the extent of imaging coverage at baseline and at subsequent follow-up time points. This will enable better consistency not only of tumour measurements but also identification of new disease.

Required anatomical regions to be imaged for assessment of tumour burden (TLs and/or NTLs) at baseline and follow-up visits vary according to the study, and these time points are specified in the SoA. Examples include the following:

- IV contrast-enhanced CT of chest-abdomen (including the entire liver and both adrenal glands) (-pelvis).
- Non-contrast CT of chest and IV contrast-enhanced abdomen (including the entire liver and both adrenal glands) (-pelvis).
- IV contrast-enhanced CT or MRI of the head and neck.
- IV contrast-enhanced MRI (preferred) or CT of the brain.

For chest-abdomen (-pelvis) imaging, the following are scanning options in decreasing order of preference, with additional options (2 to 4) for consideration when patients have sensitivity to IV contrast or have compromised renal function:

1 Chest-abdomen (-pelvis) CT with IV CT contrast (most preferred).
2 Chest CT without IV-contrast + abdomen (-pelvis) MRI with IV MRI contrast, if CT IV contrast (iodine based) is medically contraindicated at any time during the study.
3 Chest-abdomen (-pelvis) CT without IV contrast, if both IV CT and MRI contrast are medically contraindicated or the patient has compromised renal function.
4 Chest-abdomen (-pelvis) MRI with IV MRI contrast, if CT cannot be performed at any time during the study.

b. IV contrast administration: Optimal visualisation and measurement of metastases in solid tumours require consistent administration (dose and rate) of IV contrast as well as timing of scanning. An adequate volume of a suitable contrast agent should be given so that the tumour lesions are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient. Oral contrast is recommended to help visualise and differentiate structures in the abdomen and pelvis.

c. Slice thickness and reconstruction interval: It is recommended that CT or MRI scans be acquired/reconstructed as contiguous (no gap) slices with ≤ 5 mm thickness throughout the entire anatomic region of interest for optimal lesion measurements. Exceptionally, particular institutions may perform medically acceptable scans at slice thicknesses > 5 mm. If this occurs, the minimum size of measurable lesions at baseline should be twice the slice thickness of the baseline scans.

For CT 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.

In this study it is recommended that CT examinations will be used to assess tumour burden at baseline (including assessment of brain lesions at baseline in patients with no known brain metastases) and follow-up visits. CT examination with intravenous contrast media administration is the preferred method. MRI should be used where CT is not feasible, or it is medically contraindicated, for pre-existing brain metastases, and when there is a clinical suspicion of brain metastases.

X-rays

Plain X-ray
Plain X-rays may be used as a method of assessment for bone NTLs and to identify the presence of new bone lesions.

Chest X-ray
Chest X-rays will not be used for assessment of TLs as they will be assessed by CT or MRI examination. Chest X-rays can, however, be used to assess NTLs and to identify the presence of new lesions. However, there is preference that a higher resolution modality, such as CT, be used to confirm the presence of NLs.

Isotopic bone scan

Bone lesions identified on an isotopic bone scan at baseline and confirmed by CT, MRI, or X-ray at baseline should be recorded as NTLs and followed by the same method per baseline assessment (CT, MRI, or X-ray).

Isotopic bone scans may be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. NLs may be recorded in case positive hot-spots appear on a bone scan that were not present on a previous bone scan; however, a newly observed equivocal hot-spot on a bone scan that cannot be verified with correlative imaging (CT, MRI, or X-ray) of the same anatomical region shall not be the only trigger for a PD assessment at that time point.

^{18}F-Fluoro-deoxyglucose-PET/CT

^{18}F-fluoro-deoxyglucose positron emission tomography (PET)/CT scans may be used as a method for identifying new extrahepatic lesions (but not intrahepatic lesions) for RECIST 1.1 assessments according to the following algorithm: NLs will be recorded where there is

positive ^{18}F-Fluoro-deoxyglucose uptake[4] not present on baseline or prior ^{18}F-fluoro-deoxyglucose-PET scan or in a location corresponding to a NL on a companion CT/MRI collected close in time to the ^{18}F-fluoro-deoxyglucose-PET scan. The PET portion of the PET/CT introduces additional data that may bias an investigator if it is not routinely or serially performed. Therefore, if there is no baseline or prior ^{18}F-fluoro-deoxyglucose-PET scan available for comparison, and no evidence of NLs on companion CT/MRI scans, then follow-up CT/MRI assessments should continue as per the regular imaging schedule to verify the unequivocal presence of NLs.

At present, low-dose or attenuation correction CT portions of a combined ^{18}F-fluoro-deoxyglucose-PET/CT scan are of limited use in anatomically based efficacy assessments, and it is therefore suggested that they should not substitute 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 examination, is of identical diagnostic quality (with IV contrast) to a dedicated diagnostic CT scan, then the CT portion of the PET/CT can be used for RECIST 1.1 tumour assessments. Caution that this is not recommended because the PET portion of the CT introduces additional (PET) data that may bias an investigator if it is not routinely or serially performed.

Ultrasound
Ultrasound examination will not be used for RECIST 1.1 assessment of tumours as it is not a reproducible acquisition method, is subjective in interpretation, and may not provide an accurate assessment of tumour size. Tumours identified by ultrasound will need to be assessed by correlative CT or MRI anatomical scan.

Other tumour assessments

Clinical examination
Clinical examination of skin/surface lesions (by visual inspection or manual palpation) will not be used for RECIST 1.1 assessments. Tumours identified by clinical examination will need to be assessed by correlative CT or MRI anatomical scans.

Endoscopy and laparoscopy
Endoscopy and laparoscopy will not be used for tumour assessments as they are not validated in the context of tumour measurements.

4 A positive 18F-fluoro-deoxyglucose-PET scan lesion should be reported only when an uptake (eg, standard uptake value) greater than twice that of the surrounding tissue or liver is observed.

Tumour markers
Tumour markers on tumour biopsy samples will not be used for tumour response assessments per RECIST 1.1.

Cytology and histology
Histology will not be used as part of the tumour response assessment per RECIST 1.1. Cytological confirmation of the neoplastic origin of any effusion (eg, ascites, pericardial effusion, and pleural effusion) that appears or worsens during the study will not be used as part of the tumour response assessment as per RECIST 1.1.

Furthermore, an overall assessment of CR (all other disease disappears/reverts to normal) would be changed to PR if an effusion remains present radiologically.

G 1 References

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.

Appendix H Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis, including COVID 19 Outbreak

Note: Changes below should be implemented only during study disruptions due to any of or a combination 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) during which patients may not wish to or may be unable to visit the study site for study visits. These changes should only be implemented if allowable by local/regional guidelines and following agreement from the sponsor.

H 1 Reconsent of Study Patients During Study Interruptions

During study interruptions, it may not be possible for the patients to complete study visits and assessments on site and alternative means for carrying out the visits and assessments may be necessary, eg, remote visits. Reconsent should be obtained for the alternative means of carrying out visits and assessments and should be obtained prior to performing the procedures described in Appendices H 2 to H 5. Local and regional regulations and/or guidelines regarding reconsent of study patients should be checked and followed. Reconsent may be verbal if allowed by local and regional guidelines (note, in the case of verbal reconsent the ICF should be signed at the patient's next contact with the study site). Visiting the study sites for the sole purpose of obtaining reconsent should be avoided.

H 2 Rescreening of Patients To Reconfirm Study Eligibility

Additional rescreening for screen failure due to study disruption can be performed in previously screened patients. The investigator should confirm this with the designated AstraZeneca clinical lead.

In addition, during study disruption there may be a delay between confirming eligibility of a patients and either enrolment into the study or commencing of dosing with study treatment. If this delay is outside the screening window specified in in the appropriate Schedule of Assessment Table, the patient will need to be rescreened to reconfirm eligibility before commencing study procedures. This will provide another opportunity to re-screen a patient in addition to that detailed in Section 5.4. The procedures detailed in Section 5.4 must be undertaken to confirm eligibility using the same randomisation number as for the patient

H 3 Home or Remote Visit to Replace On-site Visit (where applicable)

A qualified HCP from the study site or third party vendor service will visit the patients home / or other remote location as per local standard operating procedures (SOPs), as applicable.

Supplies will be provided for a safe and efficient visit. The qualified HCP will be expected to collect information per the CSP.

H 4 Telemedicine Visit to Replace On-site Visit (where applicable)

In this appendix, the term telemedicine visit refers to remote contact with the patients using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

During a civil crisis, natural disaster, or public health crisis, on-site visits may be replaced by a telemedicine visit if allowed by local/regional guidelines. Having a telemedicine contact with the patients will allow adverse events, concomitant medication, Eastern Cooperative Oncology Group performance status (ECOG PS) to be reported and documented.

H 5 Data Capture During Telemedicine or Home/Remote Visits

Data collected during telemedicine or home/remote visits will be captured by the qualified HCP from the study site or TPV service, or by the patient themselves.

H 6 COVID-19 Risk Assessment

The safety of patients is of primary importance. Any potential risks of participating in the study, particularly with the added challenges due to COVID-19 outbreak, should be weighed against the anticipated benefit (see also principle 2.2 of ICH GCP). Investigators are advised to use clinical judgement in determining infection prevention precautions for study patients.

The emergence of SARS-CoV-2 presents a potential safety risk for cancer patients. Patients enrolling in this study may require more frequent visits to the site for study treatment administration and for study assessments compared to patients receiving standard of care. Therefore, several risk mitigation factors have been implemented related to study conduct during the COVID-19 outbreak, for patient management in an event of COVID 19, and actions to be taken on study treatment (see Appendix H 9). With these measures in place, it is considered that the anticipated potential benefits for the patients enrolled in this study outweigh the potential risks. All implemented measures prioritise trial patient safety and data validity; in case these 2 conflict with each other, trial patient safety should always prevail (see also European Medicines Agency Guidance on the management of clinical trials during the COVID-19 [coronavirus] pandemic [EMA 2020]).

Notably, patients with active COVID-19 infection confirmed by local laboratory testing will not be eligible for study enrolment (see CSP Section 5.2).

H 7 Potential Risks during COVID-19

Every effort should be made to follow the CSP. Appendix H 10 provides a dose modification and management plan for patients with confirmed or suspected COVID-19 who are being treated with study treatment ceralasertib and durvalumab. The risk-benefit assessment should be carefully considered for each patient enrolling in the study based on the known safety risks related to COVID-19, individual needs, and local guidelines and restrictions. Investigators must continue to use their best clinical judgement in determining the most optimal care for patients and utmost diligence in determining their eligibility for study participation, continued study treatment, and overall assessment of benefit/risk of study treatment or participation.

The sponsor must be promptly notified of a site's inability to perform study activities due to COVID-19 outbreak in order to minimise any potential risks.

H 8 New Patient Enrolment

Study sites may continue to recruit new patients into the study provided the following activities to preserve study integrity can be met:

- Upon discussion with the site monitor, the study site has confirmed the ability to enrol and manage new patients effectively and in compliance with the protocol.
- Data will continue to be entered into the eCRF and queries resolved in a timely manner.

Per CSP Exclusion Criterion (see CSP Section 5.2), patients with uncontrolled intercurrent illness, including but not limited to, ongoing or active infection are not eligible for the study participation and hence such patients (including those who have confirmed COVID-19) should not be included for study participation.

H 9 Study Treatment Administration

If an AE or SAE is associated with COVID-19, the investigator should determine whether the patients' treatment with the study treatment should continue, be interrupted, or be discontinued in accordance with the CSP.

AEs, SAEs, cycle delays and/or treatment suspensions associated with COVID-19 along with logistical issues should be reported according to the eCRF Completion Guidelines.

For dosing discontinuations, where applicable, the dosing discontinuation guidelines should be followed, and the End of Treatment Form(s) completed.

H 10 Ongoing Patients

Patients receiving study treatment should continue to undergo safety assessments prior to dosing in accordance with the CSP. In case it is not feasible to perform safety assessments, study treatment should be interrupted until such assessments can be completed.

H 10.1 If a Patient has an Event Suspected to be COVID-19

Delay or omit study treatment as appropriate and test for COVID-19 per local health authority or institutional guidance.

- Signs and symptoms of COVID-19 include but are not limited to new onset of fever, new or worsening cough, shortness of breath, difficulty breathing and sometimes abnormal chest imaging and may be similar to those of an imAE.
- In accordance with the CSP and the TMGs for imAEs, thorough evaluation should be performed to accurately identify the underlying pathology in case an AE is encountered for a patient.
- If COVID-19 is ruled out, study treatment may be resumed per the CSP.
- If COVID-19 is confirmed or diagnosis still suspected after evaluation, manage COVID-19 per local guidance until full recovery.

H 10.2 Patients with Confirmed COVID-19

Patients with confirmed COVID-19 (by local laboratory testing and/or combination of key symptoms) should have study treatment withheld and COVID-19 managed per local guidance.

In case of confirmed COVID-19 and a simultaneous imAE requiring treatment, investigators are advised to apply clinical judgement regarding the use of corticosteroids as per the durvalumab/tremelimumab TMGs. This includes also the consideration of alternate immunosuppressive agents other than corticosteroids for imAE management, depending on the individual patient's presentation (Curigliano et al 2020).

H 10.3 Restarting Study Treatment

Study treatment must not be resumed until recovery from COVID-19 (eg, confirmed by imaging, lab testing and/or absence of symptoms) and COVID-19-specific treatment has been completed per local guidance.

The study clinical lead should be contacted if any additional guidance or clarification is needed.

H 10.4 Vaccination Against COVID-19

Protocol restrictions applying to live attenuated vaccines are relevant for live attenuated COVID-19 vaccines as well. Investigators should apply their discretion assessing the risk benefit of other types of COVID-19 vaccines for patients in clinical trials. Ideally, administration of the vaccine should be done on a different day other than the day of study drug administration to differentiate any potential AEs seen from the vaccine and study drug. The administration of the vaccine and any potential AEs associated with the vaccine are to be documented on the concomitant medication and AE eCRFs, respectively.

H 11 References

Curigliano et al 2020
Curigliano G, Banerjee S, Cervantes A, Garassino M, Garrido P, Girard N. Managing cancer patients during the COVID-19 pandemic: an ESMO multidisciplinary expert consensus. Ann Oncol 2020;31(10):1320-35.

EMA 2020
EMA, Clinical Trials Facilitation and Coordination Group, European Commission. Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic, Version 2, 27 March 2020. Available from: URL: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf. Accessed: 17 December 2020.

Appendix I Patient Reported Outcomes

I 1 CCI

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CCI

I 2 CCI

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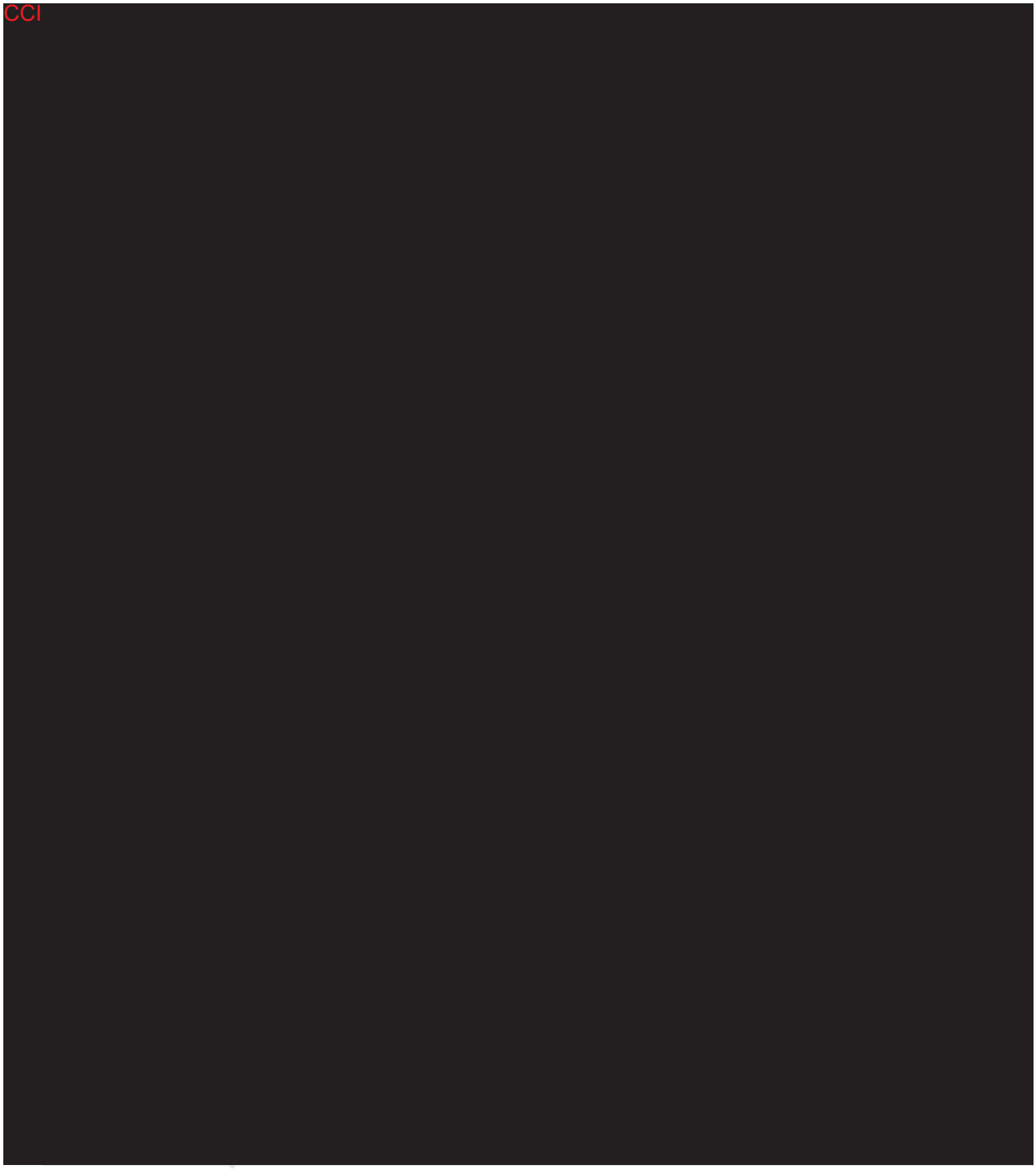

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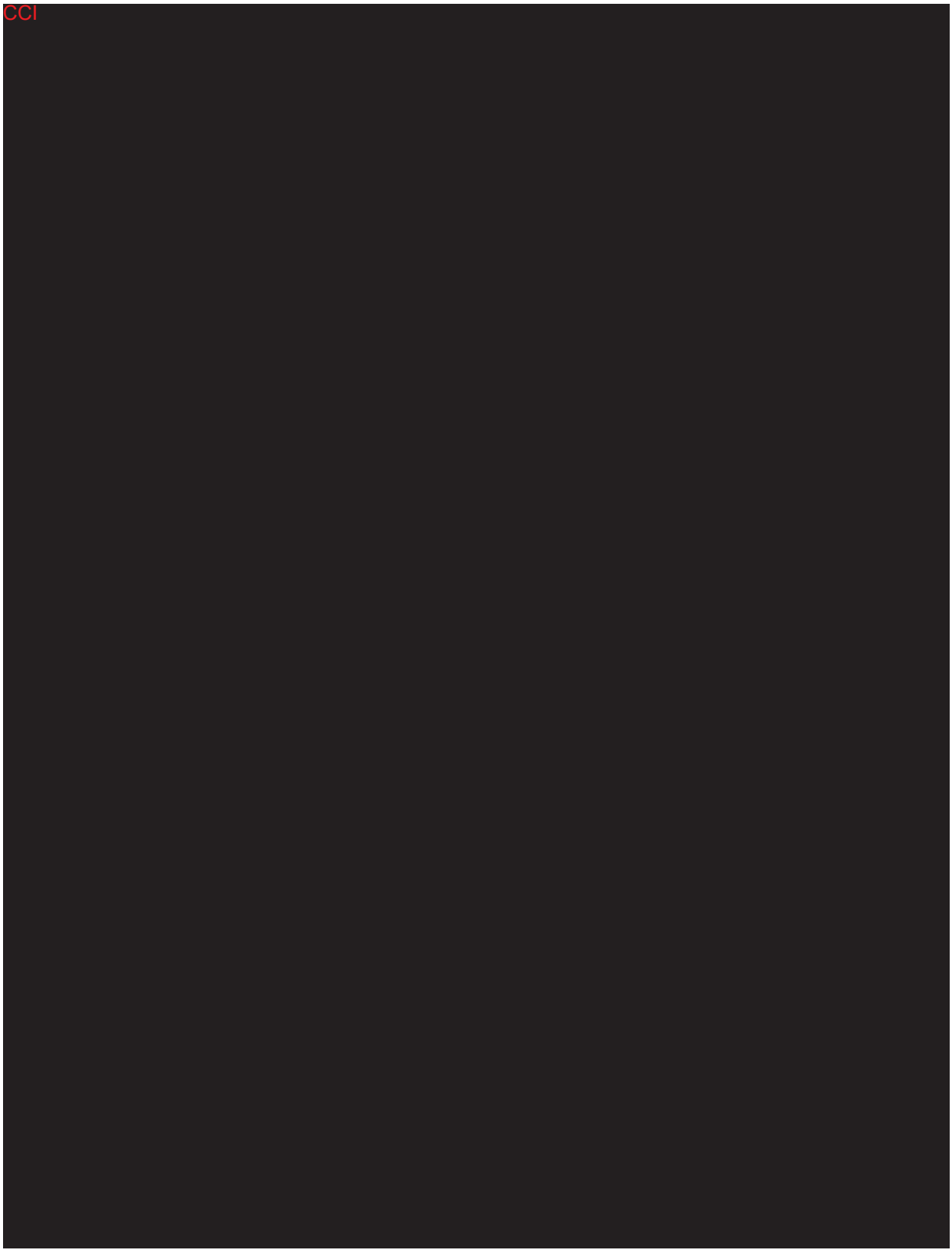

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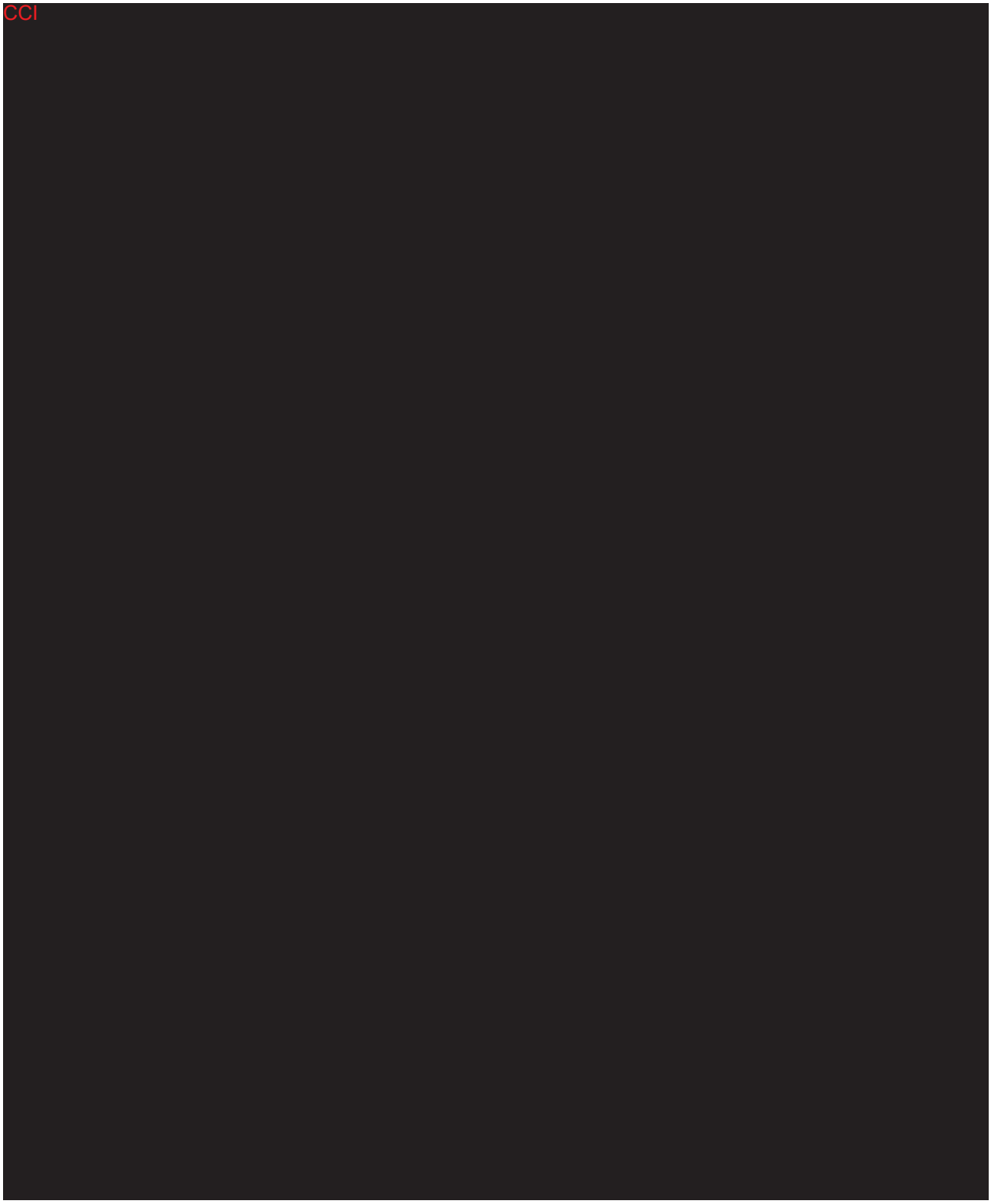

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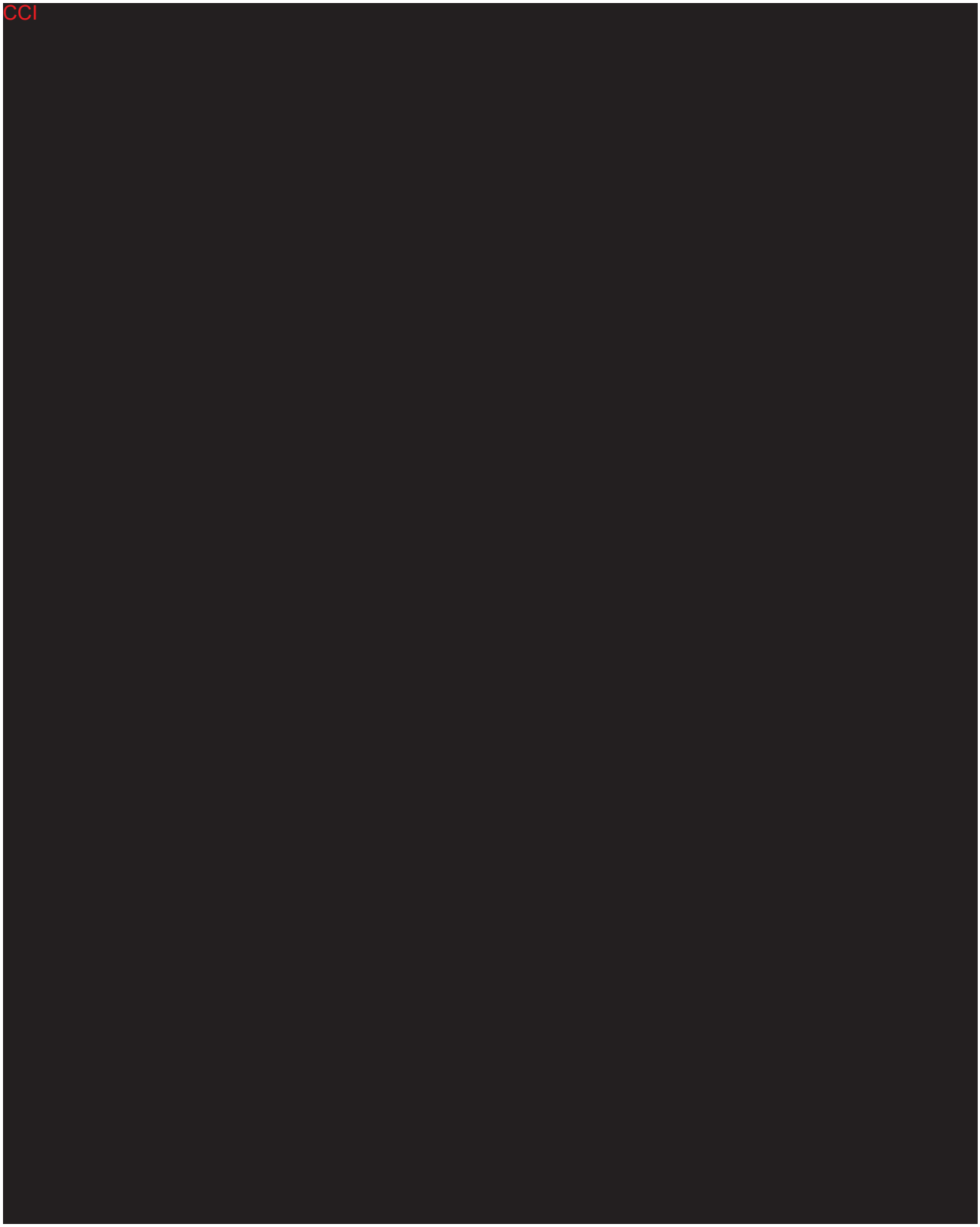

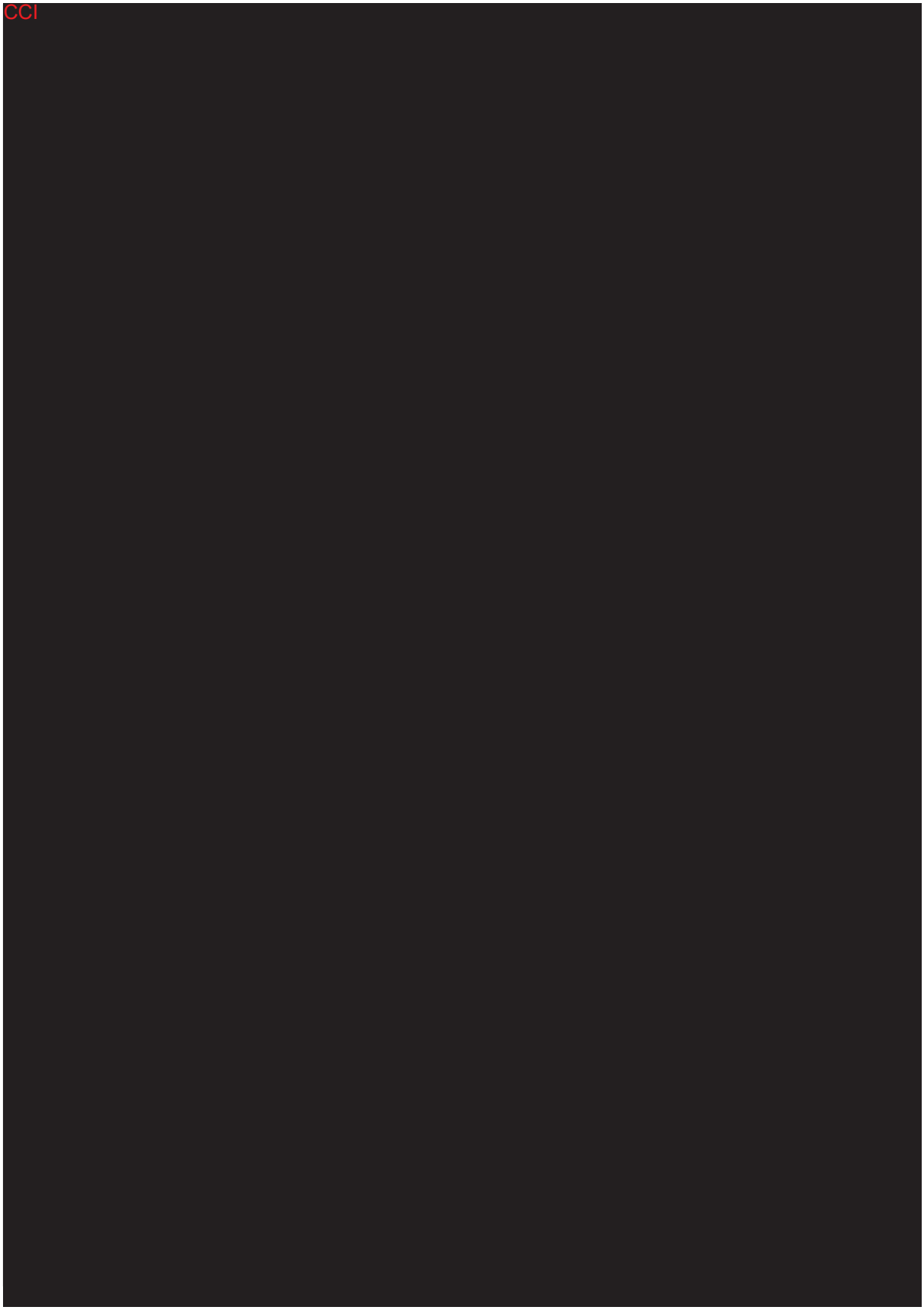
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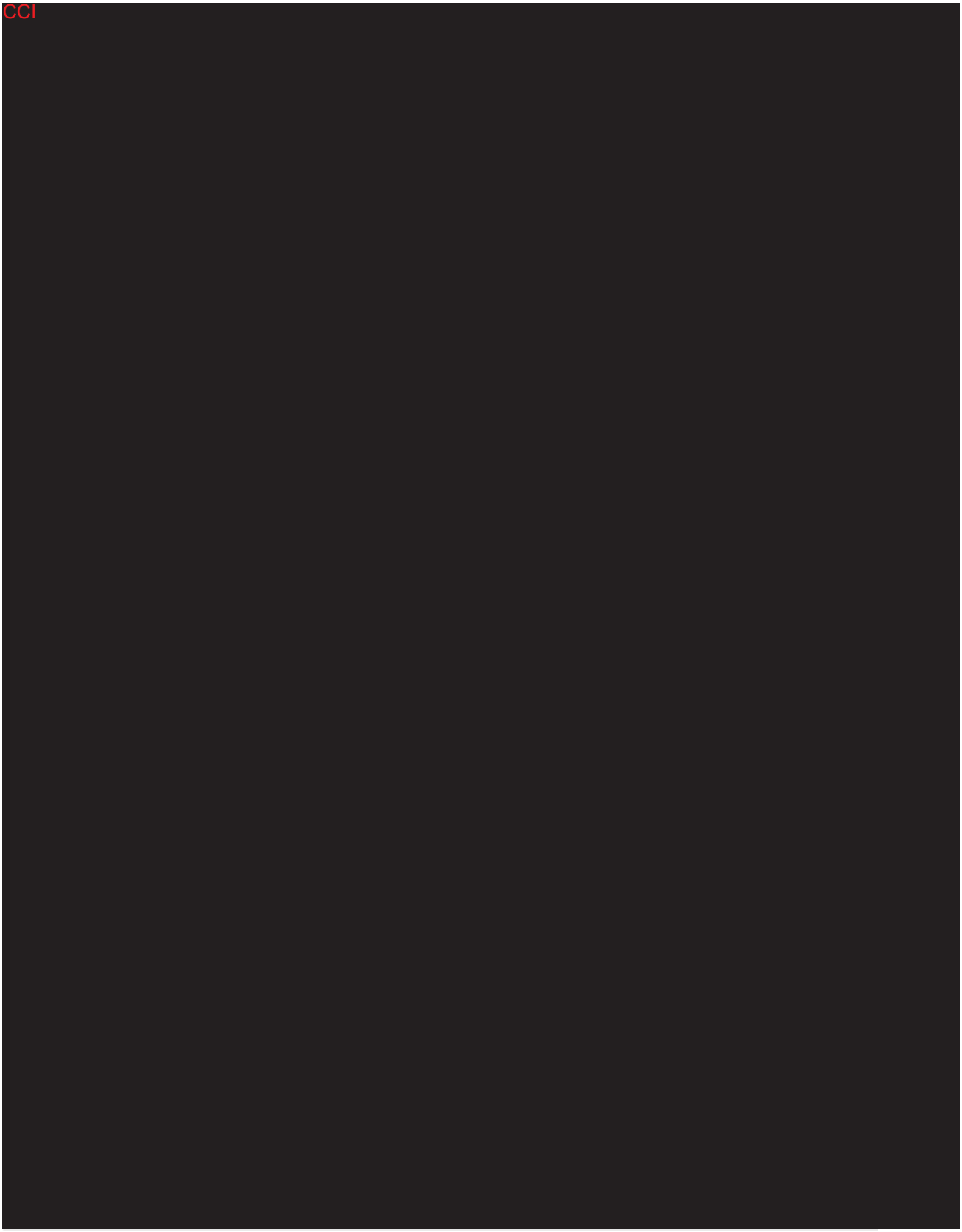
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Appendix J Abbreviations

Abbreviation or special term	Explanation
ADA	anti-drug antibody
ADE	adverse device effect
ADR	adverse drug reaction
AE	adverse event
AESI	adverse events of special interest
AIDS	acquired immunodeficiency syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase/transaminase
AML	Acute myeloid leukaemia
ANC	absolute neutrophil count
AST	aspartate aminotransferase/transaminase
ATM	ataxia telangiectasia mutated
ATR	ataxia and telangiectasia related
BCR	Binding Corporate Rules
BD	twice daily
BICR	blinded independent central review
BOR	Best Overall Response
BP	blood pressure
BRAF	B-Rapidly Accelerated Fibrosarcoma gene
BRCA	Breast Cancer gene
BRCP	Breast Cancer Resistance Protein
CAPA	corrective action preventive action
CI	confidence interval
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CPI	checkpoint inhibitors
CR	complete response
CRO	Contract Research Organisation
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CCI	CCI

Abbreviation or special term	Explanation
CTIS	Clinical Trials Information System
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
CTR	clinical trials regulation
DCO	data cut off
DES	data entry site
DILI	Drug Induced Liver Injury
DLT	dose limiting toxicity
DNA	deoxyribonucleic acid
DoR	duration of response
EAP	early access program
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
CCI	CCI
CCI	CCI
ePRO	electronic PRO
CCI	CCI
EU	European Union
CCI	CCI
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GzmB	Granzyme B
HbsAg	HBV surface antigen
HBV	hepatitis B virus
HCP	healthcare professional
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HL	Hy's Law
HR	hazard ratio
CCI	CCI
IATA	International Airline Transportation Association
IB	Investigator's Brochure
ICF	informed consent form

Abbreviation or special term	Explanation
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFN	interferon
IgG	immunoglobulin G
ILD	interstitial lung disease
imAE	immune-mediated AE
INR	international normalised ratio
IO	immune-oncology
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISG	IFN stimulated genes
IV	intravenous
IVRS/IWRS	Interactive Voice/Web Response System
KL-6	Krebs von den Lungen-6
LDH	lactate dehydrogenase
LVEF	left ventricular ejection fraction
MDS	Myelodysplastic syndrome
MEK	mitogen-activated protein kinase gene
MMRM	mixed effect model repeated measures
MoA	mechanism of action
MRI	magnetic resonance imaging
MSI	microsatellite instability
MUGA	multigated acquisition
NF1	neurofibromatosis type 1
NSCLC	non-small-cell lung carcinoma
ORR	Objective response rate
OS	overall survival
PARP	poly-adenosine 5'-diphosphate-ribose polymerase
CCI	CCI
PD-(L)1	programmed death ligand 1
PD1	programmed cell death protein 1
PFS	progression free survival
CCI	CCI

Abbreviation or special term	Explanation
CCI	CCI
CCI	CCI
PHL	Potential Hy's Law
PI	Principal investigator
PK	pharmacokinetic
PR	partial response
PRO	patient reported outcome
CCI	CCI
PTAP	Post-Trial Access Program
Q28D	every 28 days
QoL	quality of life
QTcF	QTc interval using the Fridericia formula
RECIST	Response Evaluation Criteria in Solid Tumours
RNA	ribonucleic acid
RTSM	Randomisation and Trial Supply Management
SADE	serious adverse device effect
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SoA	Schedule of Activities
SP-D	surfactant protein D
SUSAR	suspected unexpected serious adverse reaction
TBL	total bilirubin
CCI	CCI
CCI	CCI
TIL	tumour infiltrating lymphocyte
TL	target lesion
TMG	Toxicity Management Guidelines
TPV	third party vendor
TSH	thyroid stimulating hormone
TTR	time to objective response
ULN	upper limit of normal
US	United States
USADE	unanticipated serious adverse device effect
WBC	white blood cell

Abbreviation or special term	Explanation
WOCBP	women of childbearing potential

Appendix K Country-specific Requirements

K 1 European Union Requirements

K 1.1 Country-specific Requirements for Belgium

Section 1.1 (Synopsis)

Revised text

After study treatment discontinuation, all patients will be followed up for safety assessments 30 days after their last dose of study treatment for ceralasertib monotherapy or 90 days after last dose of study treatment for ceralasertib and durvalumab combination. A urine pregnancy test must be also performed for WOCBP at 6 months after last dose of study treatment (ceralasertib monotherapy or ceralasertib in combination with durvalumab). All randomised patients in the main study and all patients in the biopsy sub study will be followed for survival status and post discontinuation anti-cancer therapies.

Section 1.3 (Schedule of Activities) Table 1

Revised table

Procedure	Screening [a]	Intervention period (28-day cycles)									Post-intervention follow-up period						Details in CSP section or appendix
		Cycles 1-2				Cycle 3			C4-onwards		Study Treatment Discontinued (last dose of study treatment)	Safety follow-up (# of days after last dose)				Progression/Survival Follow-up (Q8W until 18 months, then Q12W)	
Cycle Day	**-21 to -1**	**Day 1**	**Day 7**	**Day 8**	**Day 15**	**Day 1**	**Day 7**	**Day 8**	**Day 1**	**Day 8**		**30 days**	**60 days**	**90 days**	**6 months**		
Visit window (± days)	**-**	**-**	**-**	**-**	**± 1**	**± 3**	**-**	**± 1**	**± 3**	**± 1**		**± 3**	**± 7**	**± 7**	**+ 7**		
Pregnancy test (WOCBP only) [o]	X	X				X			X			X	X	X	X		Section 8.2.5

Revised text

o Women of childbearing potential only. Serum pregnancy test at screening, urine test at other time points up to 6 months after the last dose of study treatment.

Section 1.3 (Schedule of Activities) Table 2

Revised table

Procedure	Screening [a]	Intervention period (28-day cycles)								Post-intervention follow-up period				Details in CSP section or appendix
		Cycles 1-2			Cycle 3			C4-onwards		Study Treatment Discontinued (Last dose of study treatment)	Safety follow-up		Progression/Survival Follow-up (Q8W until 18 months, then Q12W)	
Cycle Day	**-21 to -1**	**Day 1**	**Day 7**	**Day 15**	**Day 1**	**Day 7**	**Day 15**	**Day 1**	**Day 15**		**30 days after last dose**	**6 months after last dose**		
Visit window (± days)	**-**	**-**	**-**	**± 1**	**± 3**	**-**	**± 1**	**± 3**	**± 1**		**± 3**	**+ 7**	**± 7**	
Coagulation parameters [n]	X				X									Section 8.2.5
Pregnancy test (WOCBP only) [o]	X	X			X			X			X	X		Section 8.2.5

Revised text

o Women of childbearing potential only. Serum pregnancy test at screening, urine test at other time points up to 6 months after the last dose of study treatment. A urine pregnancy test must be locally performed for WOCBP 6 months after last dose of study treatment. If the pregnancy test is positive, the investigator must report it per procedures outlined in Section 8.3.13.

Section 1.3 (Schedule of Activities) Table 3

Revised table

Procedure	Screening [a]	Intervention period (28-day cycles)										Post-intervention follow-up period						Details in CSP section or appendix
		Cycle 0				Cycle 1				C2-onwards		Study Treatment Discontinued (last dose of study treatment)	Safety follow-up (# of days after last dose)				Progression/Survival Follow-up (Q8W until 18 months, then Q12W)	
Cycle Day	-21 to -1	Day 1	Day 7	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8		30 days	60 days	90 days	6 months		
Visit window (± days)	-	-	-	-	± 1	± 3	-	± 1		± 3	± 1		± 3	± 7	± 7	+ 7		
Pregnancy test (WOCBP only) [o]	X	X				X				X			X	X	X	X		Section 8.2.5

Revised text

o Women of childbearing potential only. Serum pregnancy test at screening, urine test at other time points up to 6 months after the last dose of study treatment.

Section 1.3 (Schedule of Activities) Table 3

Revised text

x Cycle 1 may start after the off-treatment biopsy is collected ie, between Cycle 0, Days 22 to 28, and if blood parameters are within limits.

Section 5.1 (Inclusion Criteria)

Inclusion criterion 16

Revised text

16 Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies (Section 5.3.1)

(a) Male patients: Male patients who intend to be sexually active with a female partner of childbearing potential must be surgically sterile or using an acceptable method of contraception (see Section 5.3.1) from the time of screening throughout the total duration of the study and 6 months after the last dose of the study treatment, (ceralasertib monotherapy and ceralasertib in combination with durvalumab), in order to prevent pregnancy in a partner. Male patients must not donate or bank sperm during this same time period.

(b) Female patients:

(i) Negative pregnancy test (serum) for women of childbearing potential.

(ii) Women of childbearing potential must agree to use one highly effective method of birth control (Table 7) from enrolment throughout the study until 6 months after last dose of study treatment (ceralasertib monotherapy and ceralasertib in combination with durvalumab). Non sterilised male partners of a woman of childbearing potential must use a male condom plus spermicide (condom alone in countries where spermicides are not approved) throughout this period.

Section 5.2 (Exclusion Criteria)

Exclusion criterion 29

Revised text

29 Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 6 months after the last dose of study treatment (ceralasertib monotherapy and ceralasertib in combination with durvalumab).

Section 5.3.1 (Contraception)

Revised text

Male patients:

Non-sterilised male patients (including males sterilised by a method other than bilateral orchidectomy, eg, vasectomy) who intend to be sexually active with male partners and women of non-child bearing potential must be using an acceptable method of contraception such as male condom plus spermicide (condom alone in countries where spermicides are not approved) from the time of screening throughout the total duration of the study and for 1 week after the last dose of study treatment to prevent exposure to ceralasertib via the semen. Where a sexual partner of a male patient is a 'woman of childbearing potential' who is not using effective contraception, or who is already pregnant, then the male patient must use a condom plus spermicide (where approved), during the study and for a further 6 months after the last dose of study treatment (ceralasertib monotherapy and ceralasertib in combination with durvalumab) to prevent pregnancy in a partner.

Female patients:

- Women of childbearing potential must use highly effective form of birth control, as defined in Table 7, from the time of signing the informed consent until 6 months after last dose of study treatment (ceralasertib monotherapy and ceralasertib in combination with durvalumab). For all women of childbearing potential, cessation of contraception after the above defined time point should be discussed with a responsible physician.

Section 7.1.2 (Follow-up of Patients Post Discontinuation of Study Treatment)

Revised text

After study treatment discontinuation, all patients will be followed up for safety assessments 30 days after their last dose of study treatment for ceralasertib monotherapy or 90 days after last dose of study treatment for ceralasertib and durvalumab combination. Patients will also be followed for survival status and post discontinuation anti-cancer therapies. A urine pregnancy test must also be performed for WOCBP 6 months after last dose of study treatment (ceralasertib monotherapy or ceralasertib in combination with durvalumab). Additional assessments to be performed at the time of the safety follow up are detailed in the SoA (Section 1.3).

Section 8.3.13.2 (Paternal Exposure)

Revised text

Pregnancy in a patient's partner(s) is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital anomaly), occurring from the date of the first dose until 180 days after the last dose and as indicated by previous studies (preclinical and clinical) should, if possible, be followed up and documented in the medical record and provided to the AstraZeneca Patients Safety data entry site. Consent from the partner must be obtained before the information is collected and reported to AstraZeneca via the Pregnancy Report Form.

K 1.2 Country-specific Requirements for France

Section 1.1 (Synopsis)

Revised text

After study treatment discontinuation, all patients will be followed up for safety assessments 30 days after their last dose of study treatment for ceralasertib monotherapy or 90 days after last dose of study treatment for ceralasertib and durvalumab combination. A urine pregnancy test must be performed for WOCBP at 6 months after their last dose of study treatment (ceralasertib monotherapy and ceralasertib in combination with durvalumab). All randomised patients in the main study and all patients in the biopsy sub study will be followed for survival status and post discontinuation anti-cancer therapies.

Section 1.3 (Schedule of Activities) Table 1

Revised table

Procedure	Screening [a]	Intervention period (28-day cycles)									Post-intervention follow-up period						Details in CSP section or appendix
		Cycles 1-2				Cycle 3			C4-onwards		Study Treatment Discontinued (last dose of study treatment)	Safety follow-up (# of days after last dose)				Progression/Survival Follow-up (Q8W until 18 months, then Q12W)	
Cycle Day	-21 to -1	Day 1	Day 7	Day 8	Day 15	Day 1	Day 7	Day 8	Day 1	Day 8		30 days	60 days	90 days	6 months		
Visit window (± days)	-	-	-	-	± 1	± 3	-	± 1	± 3	± 1		± 3	± 7	± 7	+ 7		
Pregnancy test (WOCBP only) [o]	X	X				X			X			X	X	X	X		Section 8.2.5

Revised text

o Women of childbearing potential only. Serum pregnancy test at screening, urine test at other time points up to 6 months after the last dose of study treatment.

Section 1.3 (Schedule of Activities) Table 2

Revised table

Procedure	Screening [a]	Intervention period (28-day cycles)									Post-intervention follow-up period			Details in CSP section or appendix
		Cycles 1-2			Cycle 3			C4-onwards		Study Treatment Discontinued (Last dose of study treatment)	Safety follow-up		Progression/Survival Follow-up (Q8W until 18 months, then Q12W)	
Cycle Day	-21 to -1	Day 1	Day 7	Day 15	Day 1	Day 7	Day 15	Day 1	Day 15		30 days after last dose	6 months		
Visit window (± days)	-	-	-	± 1	± 3	-	± 1	± 3	± 1		± 3	+ 7	± 7	
Pregnancy test (WOCBP only) [o]	X	X			X			X			X	X		Section 8.2.5

Revised text

o Women of childbearing potential only. Serum pregnancy test at screening, urine test at other time points up to 6 months after the last dose of study treatment. A urine pregnancy test must be locally performed for WOCBP 6 months after last dose of study treatment. If pregnancy test is positive, the investigator must report it per procedure outlines in Section 8.3.13

Section 1.3 (Schedule of Activities) Table 3

Revised table

Procedure	Screening [a]	Intervention period (28-day cycles)										Post-intervention follow-up period						Details in CSP section or appendix
		Cycle 0				Cycle 1				C2-onwards		Study Treatment Discontinued (last dose of study treatment)	Safety follow-up (# of days after last dose)				Progression/Survival Follow-up (Q8W until 18 months, then Q12W)	
Cycle Day	-21 to -1	Day 1	Day 7	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8		30 days	60 days	90 days	6 months		
Visit window (± days)	-	-	-	-	± 1	± 3	-	± 1		± 3	± 1		± 3	± 7	± 7	+ 7		
Pregnancy test (WOCBP only) [o]	X	X				X				X			X	X	X	X		Section 8.2.5

Revised text

o Women of childbearing potential only. Serum pregnancy test at screening, urine test at other time points up to 6 months after the last dose of study treatment.

Section 4.1 (Overall Design)

Revised text

Patients with BRAF mutations must have received a BRAF or BRAF plus MEK inhibitor if eligible to do so.

Section 5.1 (Inclusion Criteria)

Inclusion criterion 7

Revised text

7 No intervening treatment eg, investigational therapy is permitted between the anti-PD-(L)1 therapy and study treatment. However, patients with BRAF or c-Kit mutations that are eligible for targeted treatment, must receive the targeted treatment before or after licensed anti-PD-(L)1 therapy and prior to study entry.

Inclusion criterion 9

Revised text

9 BRAF V600E or V600K mutation status must be known at screening. Patients with BRAF mutant melanoma must have had a prior treatment regimen that included vemurafenib, dabrafenib, or an approved BRAF and approved MEK inhibitor.

Inclusion criterion 16

Revised text

10 Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies (Section 5.3.1)

(a) Male patients: Male patients who intend to be sexually active with a female partner of childbearing potential must be surgically sterile or using an acceptable method of contraception (see Section 5.3.1) from the time of screening throughout the total duration of the study and until 5 times the half-life (2.5 days) plus 6 months after the last dose of the study treatment, (ceralasertib monotherapy and ceralasertib in combination with durvalumab), in order to prevent pregnancy in a partner. Male patients must not donate or bank sperm during this same time period.

(b) Female patients:

(i) Negative pregnancy test (serum) for women of childbearing potential.

(ii) Women of childbearing potential must agree to use one highly effective method of birth control (Table 7) from enrolment throughout the study until 5 times the half-life (2.5 days) plus 6 months after the last dose of study treatment (ceralasertib monotherapy and ceralasertib in combination with durvalumab). Non sterilised male partners of a woman of childbearing potential must use a male condom plus spermicide (condom alone in countries where spermicides are not approved) throughout this period.

Section 5.2 (Exclusion Criteria)

Exclusion criterion 29

Revised text

11 Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to employ effective birth control from screening until 5 times the half-life (2.5 days) plus 6 months after the last dose of study treatment (ceralasertib monotherapy and ceralasertib in combination with durvalumab).

Section 5.3.1 (Contraception)

Revised text

Male patients:

Non-sterilised male patients (including males sterilised by a method other than bilateral orchidectomy, eg, vasectomy) who intend to be sexually active with male partners and women of non-child bearing potential must be using an acceptable method of contraception such as male condom plus spermicide (condom alone in countries where spermicides are not approved) from the time of screening throughout the total duration of the study and for 1 week after the last dose of study treatment to prevent exposure to ceralasertib via the semen. Where a sexual partner of a male patient is a 'woman of childbearing potential' who is not using effective contraception, or who is already pregnant, then the male patient must use a condom plus spermicide (where approved), during the study until 5 times the half-life (2.5 days) plus 6 months after the last dose of study treatment (ceralasertib monotherapy and ceralasertib in combination with durvalumab) to prevent pregnancy in a partner. Male patients should refrain from fathering a child or donating sperm from the start of dosing until 5 times the half-life (2.5 days) plus 6 months after the last dose of study treatment, if there is a concern about damaging the developing foetus from drug in ejaculate.

Female patients:

- Women of childbearing potential must use highly effective form of birth control, as defined in Table 7, from the time of signing the informed consent until 5 times the half-life (2.5 days) plus 6 months after last dose of study treatment (ceralasertib monotherapy and ceralasertib in combination with durvalumab). For all women of childbearing potential, cessation of contraception after the above defined time point should be discussed with a responsible physician.

Section 6.6 (Dose Modification) Table 11

Revised table

Table 11 Guidance for Dose Modifications, Interruptions, and Discontinuations for Ceralasertib (all treatment arm) and Ceralasertib plus Durvalumab

Event	Action
CCI	

Event	Action
CCI	

Section 7.1 (Discontinuation of Study Treatment)

Added text

Note that discontinuation from study treatment is NOT the same thing as a withdrawal from the study.

If patients in the combination therapy arm discontinue treatment with either one of the combination agents due to toxicity, they may continue on monotherapy with the other drug as long as they are continuing to show clinical benefit, as judged by the investigator and in the absence of discontinuation criteria.

Section 7.1.2 (Follow-up of Patients Post Discontinuation of Study Treatment)

Revised text

After study treatment discontinuation, all patients will be followed up for safety assessments 30 days after their last dose of study treatment for ceralasertib monotherapy or 90 days after

last dose of study treatment for ceralasertib and durvalumab combination. Patients will also be followed for survival status and post discontinuation anti-cancer therapies. A urine pregnancy test must also be performed for WOCBP at 6 months after their last dose of study treatment (ceralasertib monotherapy and ceralasertib in combination with durvalumab). Additional assessments to be performed at the time of the safety follow up are detailed in the SoA (Section 1.3).

Section 8.3.13.2 (Paternal Exposure)

Revised text

Non-sterilised male patients who intend to be sexually active with a female partner of childbearing potential should refrain from fathering a child or donating or banking sperm for 5 times the half-life (2.5 days) plus 6 months after the last dose of study treatment.

Pregnancy in a patient's partner(s) is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital anomaly), occurring from the date of the first dose until 5 times the half-life (2.5 days) plus 6 months after the last dose and as indicated by previous studies (preclinical and clinical) should, if possible, be followed up and documented in the medical record and provided to the AstraZeneca Patients Safety data entry site. Consent from the partner must be obtained before the information is collected and reported to AstraZeneca via the Pregnancy Report Form.

K 1.3 Country-specific Requirements for Germany

Section 1.1 (Synopsis), Section 4.1 (Overall Design), Section 9.2 (Sample Size Determination)

Revised text

Note: "Enrolled" means a patient's, ~~or their legally acceptable representative's~~ agreement to participate in a clinical study following completion of the informed consent process. Potential patients who are screened for the purpose of determining eligibility for the study, but are not randomised/assigned in the study, are considered "screen failures", unless otherwise specified by the protocol.

Section 8.3 (Adverse Events and Serious Adverse Events)

Revised text

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

Appendix A 3 (Informed Consent Process)

Revised text

- 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, and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. 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 centre.
- 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.
- Patients must be re-consented 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~~.

Appendix G (Guidelines for Evaluation of Objective Tumour Response Using RECIST 1.1 (Response Evaluation Criteria in Solid Tumours))

RECIST 1.1 evaluation of overall visit response at follow-up

Revised text

Derivation of overall visit response as a result of the combined assessment of TLs, NTLs, and NLs uses the algorithm shown in Table 19.

~~Most studies should require at least 1 TL at baseline (please see Inclusion Criteria). For these studies, please delete the rows and footer text in green font below. For studies where there is no mandatory requirement to have measurable disease at baseline and therefore it is possible to have not applicable in TLs at baseline, please retain rows and footer text in green font~~.

Appendix L Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the TOC.

Amendment 2 – 14 March 2022

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

Clinical Study Protocol Amendment 2 was prepared to update the CSP to reflect the change in ceralasertib dosing schedule, to update the randomisation ratio and the sample size, to update the language and align it with the *Durvalumab and Late Phase Oncology CSP Template*, to update data based on the ceralasertib and durvalumab IB and PSSR updates, and in response to queries from regulatory authorities.

Formatting improvements, such as updates to abbreviations and punctuation corrections, are not presented in this summary.

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Summary of Changes in Protocol Amendment 2			
Section 1.1 Synopsis, Section 1.3 Schedule of Activities, Section 2.2 Background, Section 2.3 Benefits/Risks Assessment, Section 4 Study Design, Section 5 Study Population, Section 6 Study Treatment Section 7 Discontinuation of Study Treatment and Patient Discontinuation/Withdrawal, Section 8 Study Assessments and Procedures, Section 9 Statistical Considerations, and Section 10 Supporting Documentation and Operational Considerations	The language has been updated	To align with the *Durvalumab and Late Phase Oncology CSP Template*.	Non-substantial
Section 1.1 Synopsis, Section 1.2 Schema, Section 1.3 Schedule of Activities, Section 2.3 Benefit/Risk Assessment,	Change in dosing schedule of ceralasertib, from a 14-day dosing schedule to a 7-day dosing schedule, both in	Emerging pre-clinical and clinical data from the HUDSON study and preliminary PKPD modelling of peripheral	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 4 Study Design, Section 6 Study Treatment	combination with durvalumab and as monotherapy, in the main study and biopsy sub-study.	blood markers from other ongoing studies, are supportive of the therapeutic benefit of the 7-day duration treatment	
Section 1.1 Synopsis, Section 1.2 Schema, Section 4 Study Design, Section 9 Statistical Considerations	Changes made to the sample size of the ceralasertib monotherapy arm	The sample size of ceralasertib monotherapy is revised as the clinical activity of ceralasertib 240 mg BD using a 7-day schedule has not been assessed yet in this patient population	Substantial
Section 1.1 Synopsis, Section 1.2 Schema, Section 4 Study Design, Section 6.3.1 Measures to Minimise Bias: Randomisation and Blinding, Main Study	Change in randomisation ratio	To align it with the change in sample size of the ceralasertib monotherapy arm	Substantial
Synopsis and Section 3 Objectives and Endpoints	Secondary objective added for the biopsy sub-study	To evaluate additional pharmacodynamic biomarkers of ceralasertib	Substantial
Section 1.1 Synopsis and Section 9.5 Interim Analyses	Adjustments to the triggers for CCI [redacted] analyses	The trigger for the CC interim analysis was revised to ensure this delivers contribution of components with no overlap in confidence intervals taking into consideration the revised sample size for ceralasertib monotherapy arm. The trigger for the CCI interim analysis was revised to ensure that adequate study data from approximately CCI % of the enrolled patients are available for analysis.	Substantial
Section 1.3 Schedule of activities	Update to the collection of fresh tumour biopsy at screening and at subsequent timepoints	To clarify optional on-treatment biopsies will be collected only if fresh	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
	(optional on-treatment biopsies)	tumour biopsy is available at screening.	
Section 1.3 Schedule of Activities, Section 8.2.2 Vital Signs	Respiratory rate added to vital signs assessments	Update based on a finding by an EC at one of the clinical sites in EU.	Non-substantial
Section 1.3 Schedule of Activities, Section 8.2.1 Physical Examination	Updates made to the timepoints of the physical examination and also to the language on physical examination	These changes were made as response to the questions raised by BfARM.	Non-Substantial
Section 2.2.3 Durvalumab	Exposure numbers updated	To align with the updates to the durvalumab IB	Non-substantial
Section 2.3 Benefit/Risk Assessment	Benefit-risk information updated	Based on updates to the durvalumab and ceralasertib IBs and PSSRs	Non-substantial
Section 4.3.2 Ceralasertib and Durvalumab Combination Therapy Dose Rationale	Median PFS and median OS corrected	Erroneous data were presented for median PFS and median OS from the Kwon M et al, 2021 publication, which were corrected.	Non-substantial
Section 5.1 Inclusion Criteria	Update to the inclusion criterion 5 to clarify that an archival tumour sample must be available at screening and a fresh tumour biopsy will be taken at screening if medically feasible.	To clarify that it is mandatory that an archival tumour sample of the patient is available at screening.	Substantial
Section 5.1 Inclusion Criteria	Update to the inclusion criterion 6 to state that patients must not have received any more than 2 prior regimens of approved therapy in the metastatic setting	To align with intended patient population.	Substantial
Section 5.1 Inclusion Criteria	Update to the inclusion criterion 8	To clarify that a minimum timeperiod of 14 days must be maintained between the first dose of study regimen and the last dose of BRAF/MEK inhibitors.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 5.3.1 Contraception	The duration for which the male and female patients in the study are expected to use contraception was updated.	In response to feedback from regulatory authorities to align the contraceptive requirements with the ceralasertib and durvalumab IBs.	Substantial
Section 5.3.2 Meal and Dietary Restrictions	Energy drinks added to the list of restricted foods	Based on the ceralasertib IB.	Non-substantial
Section 5.3.3 Lifestyle Considerations - Skin	Sunglasses added to the measures to be adopted by the patients to prevent prolonged exposure to the sun.	Patients in the study are expected to use sunglasses to avoid prolonged exposure to sun during the study treatment and 4 weeks after the last dose of study treatment	Non-substantial
Section 6.6 Dose Modification	Updates to the assessment timepoints for patients with ≥ Grade 3 of anaemia, neutropenia, or thrombocytopaenia later than Cycle 2	Changes are made in response to the questions raised by ANSM	Substantial
Section 6.6 Dose Modification	Updates to the table 'Guidance for Dose Modifications, Interruptions, and Discontinuations for Ceralasertib (all treatment arm) and Ceralasertib plus Durvalumab'	To align with ceralasertib PSSR update	Substantial
Section 6.5.1 Drug-Drug Interaction Between Ceralasertib and Other Drugs	Updates made to CCI metabolism impacted by ceralasertib	To align with the updates to the ceralasertib IB	Non-substantial
Section 8.3.5	MUGA scans added AEs based on examinations and tests	To align with the addition of echocardiogram/MUGA scans as other safety assessments	Non-substantial
Section 8.5.2 Immunogenicity assessment	Language updated to clarify that blood samples will be collected to evaluate immunogenicity to	To keep the language relevant to the study design	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
	durvalumab alone and not to other antigens.		
Section 9.5 Interim Analyses	Revision to the criteria for the IDMC to stop recruitment into the treatment arms	To align it with the change in sample size of the ceralasertib monotherapy arm	Substantial

Amendment 1 – 01 July 2021

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

Inclusion of updates for Amendment 1 was prepared in response to queries from the Food and Drug Administration (FDA) and Central Institutional Review Board (CIRB).

Formatting improvements, such as updates to abbreviations and punctuation corrections, are not presented in this summary.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis And 3.0 Objectives and Endpoints	Deletion of listed biomarkers in a Biopsy sub-study secondary objective and endpoint	Amended text due to previous feedback from competent authority
1.1 Synopsis And 9.4 Statistical Analysis	Clarified the analysis set for comparative analyses	In response to feedback from competent authority
1.1 Synopsis And 7.1.2 Follow-up of Patients Post Discontinuation of Study Treatment	Updated follow-up safety assessments to '30 days after last dose of study treatment for ceralasertib monotherapy or 90 days after last dose of study treatment for ceralasertib and durvalumab combination'	To align with durvalumab safety requirements and feedback from competent authority.
1.2 Schema	Edited wording on the Biopsy sub-study	To clarify treatment design.
1.3 Schedule of Activities	Additional visits (60 and 90 day) in safety follow-up in Table 1 and 3	To align with durvalumab safety requirements.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities	Added the following wording to footnotes 'o' and 'p' in Table 1 and footnotes 'l' and 'm' in Table 3: 'in all patients (at pre-dose for durvalumab dosing day)' and changed term "until" to "up to"	To clarify biomarker collection
1.3 Schedule of Activities	Added Day 8 and 15 to footnote 'r' in Table 2	To clarify PK sample collection days
1.3 Schedule of Activities Table 3	Updated activity names to 'Plasma for circulating soluble factors' and 'Serum for circulating factors'	To better align with same activities in the Main Study (Table 1)
1.3 Schedule of Activities	Updated ECOG in Table 1 and 3	To align with durvalumab safety requirements.
1.3 Schedule of Activities – Table 1 and 2- ePRO	Updated some measures in the schedule of activities to be required every 3 weeks rather than every 4 weeks	To better align with timing of treatment cycles
1.3 Schedule of Activities – Table 2- ePRO	Changed D14 to D15	To be aligned with measurement in Table 1
1.3 Schedule of Activities	Removed specification of timing for PRO administration for Table 1 and Table 2	It is not necessary to specify timing of PRO administration relative to dosing for either ceralasertib (due to 2 doses a day) or durvalumab (due to pre-specified dosing and visit schedule
3 Objectives and Endpoints	Updated the Biopsy sub-study Objectives and Endpoints	Amendment of the listed Secondary objectives and Endpoints
4.3.1 Ceralasertib Monotherapy Dose Rational	Updated ceralasertib monotherapy dose rational	Rationale updated to include findings from preliminary population PK and clarification on the sigmoid model.
5.1 Inclusion criteria	Text '> 30 kg' was added.	Clarified that weight should be above 30kg.
5.2 Exclusion criteria	Harmonization of the QTcF resting interval between male and female	In response to feedback from competent authority
5.2 Exclusion criteria	Updated total bilirubin exclusion threshold	In response to feedback from competent authority
6.1.1 Study Treatments	Added timing in Table 6 for ceralasertib treatment	To aid clarity

Section # and Name	Description of Change	Brief Rationale
6.1.1 Study Treatments	Moved a paragraph from Section 6.2.1.2 Durvalumab Infusion preparation	To aid clarity and flow
6.3 Measures to Minimise Bias: Randomisation and Blinding	Provided additional detail on stratification factors in the Main Study (Section 6.3.1)	In response to feedback from competent authority
6.5.2 Rescue Medication	Replaced original paragraph with durvalumab requirements	To align with durvalumab safety requirements.
6.6 Dose Modification	Text '> 30 kg' and ≤ 30 kg was added.	To clarify the durvalumab dose management based on patient weight.
8.2.4.2.2 CCI [redacted]	Changed from 4 to 5 items by adding "cough".	Updated according to the CCI [redacted] guidelines.
8.3 Adverse Events and Serious Adverse Events	Extended AE/SAEs collection to 90 days after last dose of study treatment for ceralasertib and durvalumab combination	To align with durvalumab safety requirements.
8.3.11 Safety Data to be Collected Following the Final Data Cut Off of the Study	Extended safety data collection to 90 days after last dose of study treatment for ceralasertib and durvalumab combination	To align with durvalumab safety requirements.
8.3.13 Pregnancy	Removed word 'not' and repetitive sentence	Clarifying that women of childbearing potential are eligible for study inclusion.
8.3.13 Pregnancy	Clarification: Pregnancy of the partner of male patient should be reported to AstraZeneca	To align with Section 8.3.13.2
8.5.2 Immunogenicity Assessments	Added extra immunogenicity assessment at 90 days and 6 months after last dose for ceralasertib and durvalumab combination	To align with durvalumab safety requirements.
8.8 Tumour Biopsies for Main and Biopsy sub-study	Added mandatory archival tumour tissue collection in the Main Study. Clarified in the biopsy sub-study section that additional tumour tissue collection is 'optional'	To better align with the schedule of assessments.

Section # and Name	Description of Change	Brief Rationale
8.10.1.6 CCI [redacted]	CCI [redacted]	Edit title for clarification
8.10.1.7 CCI [redacted]	CCI [redacted]	Edit title for clarification
9.2.1 Main Study	Provide sample size justification for secondary objective to compare treatment arms for ORR.	In response to feedback from competent authority
Table 13 Populations for Analysis	Clarified the analysis set for comparative analyses	In response to feedback from competent authority
Appendix I2 CCI [redacted]	CCI [redacted]	CCI [redacted]

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