STATISTICAL ANALYSIS PLAN

Sponsor:	AstraZeneca	Protocol/CIP Number:	D6185C00001/Multiple drugs
CIL Project Number:	40773		

Protocol No. D6185C00001

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

Statistical Analysis Plan

Prepared for:
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Version 9.0 Date 15 February 2024

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CIL Project Number:	40773		

VERSION HISTORY OF IMPLEMENTED PLANS

Version	Date	Revision Author	Comments
1.0	04-Jul-2019	PPD	
2.0	04-Jul-2019		No difference between versions 1.0 and 2.0. Version 2.0 was signed in ANGEL.
3.0	16-Oct-2020		Implementing the CSP v6 and adding details regarding Modules 6 and 7. Additional details for re-allocated subjects and safety population flag.
4.0	01-Apr-2021		Implementing the changes as discussion based on Module 2 dry-run outputs. Updates to the following sections:(1) Section 5.2: Change in the TEAE definitions, change in planned reporting for PK and added, update to Table 4 defining the overall visit responses. (2) Section 6.3.2: Include local biomarker results in case of missing central biomarker results taking into account the protocol version in which the patients were enrolled. Fine-tune other rules for the classification. (3) Section 6.4.3.2.3: Addition of CCI [redacted] (4) Section 6.4.3.7: Correction of indentation of "No Progression". (5) Section 6.5.2: Update to TEAE definitions and to the 90-day follow-up period considerations.

Sponsor:	AstraZeneca	Protocol/CIP Number:	D6185C00001/Multiple drugs
CIL Project Number:	40773		

Version	Date	Revision Author	Comments
			(6) Section 6.5.4.1: Remove the post-dose visit details for Module 2. (7) Section 6.5.4.2: Clarify how ECG would be calculated for 'triplicates'. (8) Section 6.6.3: Add details that durvalumab data will be reported at end of study. (9) Section 7.1: Add a bullet to handle data in case they are reported to 4 or more decimals, other details for extent of lab, ECG, VS data to be included in displays and additional COVID-19 outputs. (10) Section 7.3.3.1: Update as per latest IDMC charter. (11) Section 7.3.3.2: Update to align with protocol. (12) Section 8.3.2: Update vital signs for module 2. (13) Section 8.4.2: Include details with definition of time from last prior immunotherapy to first dose of study drug and duration in days for last prior immunotherapy, duration of smoking history. (14) Section 8.5.1: Add details to handle if ATC level 4 is missing. (15) Section 8.6.2.2 add swimmer plot of [redacted] (16) Section 8.7.2: Fine-tune certain summaries presentation.

Sponsor:	AstraZeneca	Protocol/CIP Number:	D6185C00001/Multiple drugs
CIL Project Number:	40773		

Version	Date	Revision Author	Comments
			(17) Section 8.7.2.3.1: Add details for log transformation for certain parameters and detail that clinical significance for local labs only will be added to the listings. (18) Section 8.7.2.3.2: Revise rule for selecting subjects to include in patient-level summaries of Hy's Law laboratory evaluations. (19) Section 8.8.1: CCI [redacted]
5.0	09-Nov-21	PPD	Implementing the CSP version 7.0, v8.0 and v9.0 (1) Section 3.3: Update of safety endpoint and add other safety assessments. (2) Section 3.4: CCI [redacted] (3) Section 4.1: Add 2 new modules, module 8 (AZD6738 monotherapy (ceralasertib)) and module 9 (Durvalumab + AZD6738 (ceralasertib)). (4) Section 4.3: Add sample size for module 9. (5) Section 5.2: Remove few changes from the analyses planned from the protocol. (6) Section 6.2.4 Add additional period for safety to be used for selected summaries of patient deaths.

Sponsor:	AstraZeneca	Protocol/CIP Number:	D6185C00001/Multiple drugs
CIL Project Number:	40773		

Version	Date	Revision Author	Comments
			(7) Section 6.4.1.1 Add information about biopsies which should not be included as intervention unless specify by the investigator. (8) Section 6.4.3.1 Add imputed death date among the latest date possible for overall survival calculation. (9) Section 6.4.3.2.2: Update of the Disease Control rate definition for module 3. (10) Section 6.5.1: Add exposure information for module 8 and 9. (11) Section 6.5.2.3: Add Covid-19 infection events section. (12) Section 6.5.3: Complete information for clinical laboratory evaluations of module 7. (13) Section 6.5.4.1: Update for module 2 and remove details for Modules 3 and 6. (14) Section 6.6.2: CCI [redacted] (15) Section 7.1 Provide information how the listings for re-allocated subjects (second cohort data) will be presented. (16) Section 7.1.1 Add listing of subjects with issues reported due to Covid-19.

Sponsor:	AstraZeneca	Protocol/CIP Number:	D6185C00001/Multiple drugs
CIL Project Number:	40773		

Version	Date	Revision Author	Comments
			(17) Section 7.3.1 Add imputation rules for specific cases with partial AE date. (18) Section 7.3.3 Add new section for imputation of death date. (19) Section 7.3.4.1: Update data monitoring section. (20) Section 7.3.4.2: Add module 9 information for interim analysis. (21) Sections 8.1 and 8.3: Update of the enrolled patients and safety analysis set definition. (22) Sections 8.6.2.1 and 8.6.2.6 Kaplan-Meier summary and plot will be presented across all cohort for OS and PFS respectively. (23) Section 8.7.2: Add a listing for subjects with confirmed/suspected COVID-19 infection. (24) Section 8.7.2.1: Add Additional Information for death categories. (25) Section 8.7.3.2 Time points collected for vital signs not as per protocol will be removed from summary but provide in listing. (26) Section 8.8.1: CCI [redacted]

Sponsor:	AstraZeneca	Protocol/CIP Number:	D6185C00001/Multiple drugs
CIL Project Number:	40773		

Version	Date	Revision Author	Comments
			(27) Section 8.8.2: CCI [redacted]
6.0	07-Jul-22	PPD	(1) Section 3.4: Add new objective following CSP v10.0. (2) Sections 4.1, 4.2, 4.3, 6.2.1, 6.3.2, 6.4.2, 6.4.3.2, 6.4.3.5, 6.5.1, 6.6.2, 7.1, 7.3.6.2, 8.6, 8.8.1 and 11: Add information about new Module 10. (3) Section 6.2.2: Per CSP v10.0, re-allocation of patients to a different treatment cohort is no longer available. (4) Section 4.3: To align with CSP v10.0, there is an increase of sample size for each biomarker non-matched cohort in Module 3 and no further recruitment to Module 8 or Module 9. (5) Section 6.4.1: CCI [redacted] (6) Sections 6.5.2.1, 8.5.1, 8.7.2 and 11: Add information related to AESI/AEPI and imAE. (7) Section 6.5.3: Update of laboratory parameters: eosinophil and monocyte counts have been added, in relation to the expanded cohorts for Module 3, and bicarbonate removed. (8) Sections 6.6.1, 8.6.2.1: Screen failed patients who were screened before protocol version 10.0 will be followed-up for survival until implementation

Sponsor:	AstraZeneca	Protocol/CIP Number:	D6185C00001/Multiple drugs
CIL Project Number:	40773		

Version	Date	Revision Author	Comments
			of protocol version 10.0. Screen failed patients who were screened after implementation of protocol version 10.0 will not be follow-up for survival. (9) Section 7.1: Add information about ongoing patients after the data cut-off and remove timing of screen failure patient analyses. (10) Sections 7.1, 8.3: Clarification relating to non-production of listings if there are no re-allocated subjects in the associated analysis set and relating to definition of analysis sets for re-allocated subjects. (11) Section 7.3: Add new imputation rules for EOT dates, subsequent cancer therapy start date and diagnosis date, laboratory values and update for imputation of adverse event/ concomitant medication stop date. (12) Section 7.3.7.2 Add information about IA. (13) Sections 7.4, 8.4.2, 8.5.2, 8.6.2.1: Update summary/listing planned for screen failure patients. (14) Section 8.2: Update protocol deviations and provide the list of category for IPD. (15) Section 8.4.2 Provide correction or additional information for few definitions.

Sponsor:	AstraZeneca	Protocol/CIP Number:	D6185C00001/Multiple drugs
CIL Project Number:	40773		

Version	Date	Revision Author	Comments
			(16) Section 8.6: CCI [redacted] (17) Section 8.7.3.5: Update the planned analyses for visual acuity
7.0	07-Feb-23	PPD	(1) Sections 2, 4.1: Add group C molecular aberration independent patient population. (2) Sections 4.1, 4.3, 6.3.2, 6.5.1, 6.5.3, 6.6.3, 7.3.8.2, 8.6, 8.8.2 and 11: Add information about new Module 11. (3) Section 4.3: Update of the sample size section. (4) Section 5.2.4: SAP changes from the CSP version 11.0. (5) Sections 7.1 and 11: efficacy endpoints will be summarised by resistance assigned by the investigator. (6) Section 7.3.4: New section specific to imputation of EOT dates. (7) Section 7.3.8.2: First IA for Module 10 is removed. (8) Section 8.4.2: Add smoking calculation rule. (9) Section 8.5.1: Remove specific imAE listing. (10) Section 8.7.2: Remove infusion related/hypersensitivity reaction for the specific AESI/AEPI/imAE outputs. (11) Section 8.8.1 Add dose regimen for Module 10 outputs. (12) Add selecting outputs for IA modules 10 and 11.
8.0	11-Jul-23	PPD	(1) In cover page and signature page: change author name by PPD.

Sponsor:	AstraZeneca	Protocol/CIP Number:	D6185C00001/Multiple drugs
CIL Project Number:	40773		

Version	Date	Revision Author	Comments
			(2) Section 3.4: Add in a footnote that AZD6738 is also known as ceralasertib (3) Section 4.2: Correction by figure 4 for reference to core CSP for cohort naming. (4) Section 4.3: Add that as per protocol version 12.0, all three cohorts in Module 3 have been closed for enrolment. (5) Section 5.2: add an introduction to explain changes in subsections are not cumulative. (6) Section 5.2.5: SAP changes from the CSP version 12.0. (7) Sections 6.4.3.2.1, 6.4.3.2.2: Update Disease Control Rate (DCR) definition to have consistency with CCI [redacted] (8) Section 7.1: Add details about management data of patients from module 11 who will go onto the combination therapy after disease progression. (9) Section 7.3.8.2: Add that per protocol version 10.0, all three cohorts in Module 3 were expanded and per protocol version 12.0, they have been closed for enrolment. (10) Sections 8.6.1, 8.6.2.3, 8.6.2.4, 8.6.2.5: add analysis using Evaluable for Confirmed Response analysis set for interim analyses when relevant to be consistent with other sections. (11) Section 8.7.3.7: New section "Interstitial Lung Disease (ILD) (module 6)" added to describe 2 listings. (12) Section 8.8.1: CCI [redacted] (13) Section 11: for interim analysis replace Evaluable for Response analysis set" by "Evaluable for Confirmed Response analysis set".

Sponsor:	AstraZeneca	Protocol/CIP Number:	D6185C00001/Multiple drugs
CIL Project Number:	40773		

Version	Date	Revision Author	Comments
			(14) Section 11: 2 listings added for ILD. Add "Requested for M11 futility analysis" to flag the 17 selected outputs for this analysis.
9.0	15-Feb-24	PPD	(1) Section 5.2.6: Noted items in SAP version 9 that are changes from CSP version 13. (2) Section 6.4.3.2.3: clarify that the censoring rule is the same as for progression-free survival described in Section 6.4.3.5. (3) Section 6.4.3.3: CCI [redacted] (4) Section 6.5.1: - Update the durvalumab total treatment duration formula for Module 6. - Clarify that actual cumulative dose is calculated up to the minimum of the following dates: date of last dose date where dose > 0, date of death, date of DCO. (5) Section 6.5.2: Add definition of TEAE for subjects from Module 11 who switch from ceralasertib monotherapy to combination ceralasertib + durvalumab. (6) Section 6.5.3: update the list of parameters for CTCAE grading (Table 10) (7) Section 6.5.4.1.2: For home BP measurements, clarify which observations will be excluded from analysis. (8) Section 7.1: - Clarify for Module 11 patients who go into combination ceralasertib + durvalumab what

Sponsor:	AstraZeneca	Protocol/CIP Number:	D6185C00001/Multiple drugs
CIL Project Number:	40773		

Version	Date	Revision Author	Comments
			data is to be taken into account/presented for laboratory, ECG and vital signs data. (9) Sections 8.1 and 8.3: Clarify the definition of enrolled subjects. (10) 8.7.2: Add rules in case several actions taken are entered in AE forms. (11) 8.7.2.1: In Table 14, update "additional information" for categories "AE with outcome of death only" and "AE with outcome of death only (AE start date falling after the 90 day follow-up period)" for patients from Module 11 who go into combination therapy: ceralasertib + durvalumab. (12) 8.7.2.3.1: Clarify that parameters with at least one zero value will not have geometric statistics calculated. (13) 8.7.3.7: Add summary analysis of ILD events that were submitted to the ILD adjudication committee. (14) 8.8.3: Specify that all data from local laboratory tests and central laboratory tests will be provided in analyses. Also add details on the biomarker analyses.

STATISTICAL ANALYSIS PLAN

Sponsor:	AstraZeneca	Protocol/CIP Number:	D6185C00001/Multiple drugs
CIL Project Number:	40773		

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STATISTICAL ANALYSIS PLAN

Sponsor:	AstraZeneca	Protocol/CIP Number:	D6185C00001/Multiple drugs
CIL Project Number:	40773		

Table of Contents

STATISTICAL ANALYSIS PLAN

Sponsor:	AstraZeneca	Protocol/CIP Number:	D6185C00001/Multiple drugs
CIL Project Number:	40773		

List of Tables

Sponsor:	AstraZeneca	Protocol/CIP Number:	D6185C00001/Multiple drugs
CIL Project Number:	40773		

1 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or special term	Explanation
ACQ	Acquired resistance
ADA	Anti-drug antibodies
AE	Adverse event
AESI	Adverse event of special interest
AEPI	Adverse event of possible interest
ALC	Absolute lymphocyte count
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AM	Ante Meridiem
ANC	Absolute neutrophil count
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
ATM	Ataxia telangiectasia mutated
B2M	Beta-2 microglobulin
BMI	Body Mass Index
BD	Twice daily
BoR	Best objective response
BP	Blood Pressure
BRCA	Breast cancer associated gene
BUN	Blood urea nitrogen
CHF	Congestive heart failure
CI	Confidence interval
CM	Concomitant Medication

Sponsor:	AstraZeneca	Protocol/CIP Number:	D6185C00001/Multiple drugs
CIL Project Number:	40773		

Abbreviation or special term	Explanation
COVID-19	Coronavirus disease 2019
CPT	Clinical program team
CR	Complete response
CRF	Case Report Form
CRP	C-reactive protein
CSP	Clinical study protocol
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CCI	[redacted]
DBL	Database lock
DBP	Diastolic blood pressure
DCO	Data cut-off
DCR	Disease control rate
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DoR	Duration of response
ECD	Early Clinical Development
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EOT	End of treatment
Eqv	Equivalent
ETDRS	Early Treatment Diabetic Retinopathy Study
eCRF	Electronic case report form

Abbreviation or special term	Explanation
FDA	Food and Drug Administration
geomean	Geometric Mean
GGT	Gamma glutamyl transferase
GRIm	Gustave Roussy Immune Score
HER2	Human epidermal growth factor receptor 2
HL	Hy's Law
HRR	Homologous recombination repair gene
IA	Interim Analysis
ICF	Informed consent form
IDMC	Independent Data Monitoring Committee
IE	Inclusion or exclusion
ILD	Interstitial Lung Disease
imAE	Immune-mediated adverse event
INR	International normalised ratio
IO	Immuno-oncology
IP	Investigational product
IPD	Important protocol deviation
IQR	Interquartile range
ITT	Intention to treat
IV	Intravenous
KM	Kaplan Meier
LD	Longest diameter
LKB1	Liver kinase B1
LLOQ	Lower limit of quantification
LRV	Lower Reference Value
LVEF	Left ventricular ejection fraction

Abbreviation or special term	Explanation
MAF	Mutant Allelic Fraction
MedDRA	Medical Dictionary for Regulatory Activities
MHC-I/II	Major histocompatibility class I/II
MRI	Magnetic resonance imaging
MUGA	Multi-gated acquisition
NA	Not Applicable
NCI	National Cancer Institute
NE	Not evaluable
NHP	Non-compliance Handling Plan
NSCLC	Non-small cell lung cancer
NTL	Non-target lesion
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed cell death-1
PD-L1	Programmed cell death ligand 1
PE	Physical examination
PFS	Progression-free survival
PHL	Potential Hy's Law
PK	Pharmacokinetics
PKAS	Pharmacokinetics analysis set
PM	Post meridiem
PR	Partial response
PRI	Primary resistance
PT	Preferred Term
Q1	First quartile

Sponsor:	AstraZeneca	Protocol/CIP Number:	D6185C00001/Multiple drugs
CIL Project Number:	40773		

Abbreviation or special term	Explanation
Q3	Third quartile
QR	Quarterly Review
QTcF	QT interval corrected for heart rate (Fridericia correction)
RBC	Red blood cell
RDI	Relative dose intensity
RECIST 1.1	Response Evaluation Criteria in Solid Tumours, version 1.1
RMH	Royal Marsden Hospital
ROS1	c-ros oncogene 1
RNA	Ribonucleic acid
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Stable disease
SD	Standard Deviation
SDV	Source data verification
SI	International system of units
SoA	Schedule of Activities
SOC	System Organ Class
SRC	Safety Review Committee
TBL	Total bilirubin
TEAE	Treatment emergent adverse events
TFL	Table Figure Listing
TNM	Tumour, nodes and metastases
TL	Target lesion
TSH	Thyroid stimulating hormone

Abbreviation or special term	Explanation
TV	Target Value
ULN	Upper limit of normal
ULOQ	Upper limit of quantification
UN/UNK	Unknown
UPC	Urinary protein/creatinine ratio
WBC	White blood cell
WHO	World Health Organization
WHO-DDE+HD	WHO-Drug Dictionary Enhanced + Herbal Dictionary

Sponsor:	AstraZeneca	Protocol/CIP Number:	D6185C00001/Multiple drugs
CIL Project Number:	40773		

2 INTRODUCTION

As described in Section 2.2 of the core Clinical Study Protocol (CSP), immune checkpoint inhibitors targeting the anti-programmed cell death-1 (PD-1)/anti-programmed cell death-ligand 1 (PD-L1) pathway have shown significant activity in the first- and second-line treatment settings in patients with advanced non-small cell lung cancer (NSCLC). However, it is becoming evident that there is a new and significant patient population emerging that does not respond to anti-PD-1/PD-L1 containing therapy (primary resistance) or progresses during anti-PD-1/PD-L1 containing therapy (acquired resistance). There is currently no established therapy for patients who have developed resistance to PD-1/PD-L1 and having been exposed to platinum-doublet therapies, and novel treatments for these patients are urgently needed.

The aim of this umbrella study (D6185C00001) is to investigate multiple study drugs for the treatment of advanced NSCLC in molecularly matched and non-matched patient populations after failure of immune checkpoint inhibitors and in the molecular aberration independent patient population, and to identify patient populations who may respond favourably to novel anti-tumour therapies. This analysis plan includes the below CSP amendments and provides the detailed description of the statistical analyses

- CSP version 7.0 dated 21 May 2020
- CSP version 8.0 dated 11 September 2020
- CSP version 9.0 dated 14 May 2021
- CSP version 10.0 dated 12 April 2022
- CSP version 11.0 dated 16 August 2022
- CSP version 12.0 dated 01 March 2023
- CSP version 13.0 dated 14 December 2023

3 STUDY OBJECTIVES

3.1 Primary Objectives

Primary objective:	Endpoint/variable:
To obtain an assessment of the efficacy of each treatment by evaluation of objective response rate	Objective response rate (ORR) based on Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST 1.1)

3.2 Secondary Objectives

Secondary objective:	Endpoint/variable:
To assess the efficacy of each therapy by evaluation of tumour response (Disease control rate, Best percentage change in tumour size, Duration of response, Progression-free survival) and Overall survival	Overall Survival (OS) Endpoints based on RECIST 1.1 including: • Disease control rate (DCR) • Best percentage change in tumour size • Duration of response (DoR) • Progression-free survival (PFS)

3.3 Safety Objectives

Safety objective:	Endpoint/variable:
To assess the safety and tolerability of each treatment	Physical examinations, laboratory findings, vital signs and other safety assessments as specified. Adverse events (AEs)/serious adverse events (SAEs) collected throughout the study, from informed consent until the safety follow-up visit

3.4 Exploratory Objectives

Exploratory objectives:	Endpoint/variable:
To investigate changes in tumour burden using CCI [redacted] levels in plasma	Collection of plasma samples to include, but not limited to, extraction of CCI [redacted] for investigation of blood-borne cancer biomarkers. Mutant Allelic Fraction (MAF) will be measured in pre-dose and serial (post-dose) plasma samples. The results of this exploratory biomarker research will not form part of the clinical study report (CSR).

STATISTICAL ANALYSIS PLAN

Sponsor:	AstraZeneca	Protocol/CIP Number:	D6185C00001/Multiple drugs
CIL Project Number:	40773		

Exploratory objectives:	Endpoint/variable:
To investigate cancer-relevant immune status	Exploratory biomarker analyses of blood and tissue samples, or utilisation of residual samples, for the analysis of tumoral and peripheral biomarkers, may include (but are not limited to) the presence of or changes in levels of RNA, DNA; epigenetic or mutational profiles or signatures; gene or protein expression profiles (eg, PD-L1, B2M, MHC-I, MHC-II); and the number, phenotype, and expression profile of immune cells. The results of this exploratory biomarker research will not form of the CSR.
To quantify CCI with the aim of characterizing CCI	To study therapeutic response/resistance using radiomic analyses of non-invasive medical images extracted from tumour evaluation images (where available) of each measurable lesion to obtain lesion phenotype dynamics in complement to CCI dynamics. The results of this exploratory research will not form part of the CSR.
To investigate changes in cancer-related gene mutations and aberrations	Relationship between genomic and genetic aberrations and response based on molecular profile of archival tumour biopsy (where available), pre-dose biopsies, tissue biopsies taken during treatment or at disease progression, and liquid biopsies. The results of this exploratory biomarker research will not form part of the CSR.
To collect and store DNA, derived from a blood sample, for future exploratory research into genes/genetic factors that may influence response e.g. distribution, safety, tolerability and efficacy of study treatments (optional)	Correlation of polymorphisms with variations in safety or response parameters to study drugs. The results of this exploratory biomarker research will not form part of the CSR.

Sponsor:	AstraZeneca	Protocol/CIP Number:	D6185C00001/Multiple drugs
CIL Project Number:	40773		

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

Note: per investigator brochure, AZD9150 is also known as danvatirsen, AZD6738 is also known as ceralasertib.
[a] From protocol v10.0 implementation, collection of survival follow-up data for screen failed patients is no longer required as sufficient data have now been collected to investigate the outcome in patients who screen fail.

4 STUDY DESIGN

4.1 General Design

This is an open-label, multi-centre, umbrella Phase II study in patients who have received an anti-PD-1/PD-L1 containing therapy and a platinum-doublet regimen for locally advanced or metastatic NSCLC either separately or in combination. The patient must have had disease progression on a prior line of anti-PD-1/PD-L1 therapy. The general study design is summarised in Figure 1 of the core CSP.

Sponsor:	AstraZeneca	Protocol/CIP Number:	D6185C00001/Multiple drugs
CIL Project Number:	40773		

This study is modular in design, consisting of treatment modules with allocation to different cohorts "matched" within each module according to different tumour molecular profiles (biomarker aberration) or biomarker "non-matched" prospectively stratified by their prior response to checkpoint immunotherapy or a molecular aberration independent group. Efficacy, safety, and tolerability will be investigated for individual cohorts within each treatment module.

The statistical methods described in the statistical analysis plan (SAP) will be performed on the following starting modules and cohorts of the study.

Table 1: Cohorts within modules of treatment

Module	Combination therapy	Group A cohort (biomarker matched)	Group B cohort (biomarker non-matched)	Group C molecular aberration independent
Module 1	Durvalumab + olaparib (AZD2281)	A.1.HRR and A.1.LKB	B.1.PRI and B.1.ACQ	NA
Module 2	Durvalumab + AZD9150 (danvatirsen)	NA	B.2.PRI and B.2.ACQ	NA
Module 3	Durvalumab + AZD6738 (ceralasertib)	A.3.ATM	B.3.PRI and B.3.ACQ	NA
Module 4	Durvalumab + vistusertib (AZD2014)	A.4.RIC	NA	NA
Module 5	Durvalumab + oleclumab (MEDI9447)	A.5.73H	B.5.PRI and B.5.ACQ	NA
Module 6	Durvalumab + trastuzumab deruxtecan (DS-8201a)	A.6.HER2e and A.6.HER2m	NA	NA
Module 7	Durvalumab + cediranib (AZD2171)	NA	B.7.ACQ	NA
Module 8	AZD6738 monotherapy (ceralasertib)	A.8.ATM	NA	NA
Module 9	Durvalumab + AZD6738 (ceralasertib)	NA	B.9.PRI and B.9.ACQ	NA
Module 10	Durvalumab + AZD6738 (ceralasertib)	NA	NA	C.10.160 and C.10.240
Module 11	AZD6738 (ceralasertib) monotherapy	NA	NA	C.11.240

The study treatment handling and administration details are described in Section 6 of the module-specific protocol appendices.

4.1.1 Safety run-in period for Module 6 only

For Module 6, there will be a safety run-in period. The purpose of the safety run-in is confirmation of the dose of trastuzumab deruxtecan and durvalumab in combination. In this safety run-in phase,

approximately 6 patients will be followed for 2 cycles to assess safety. The study procedures and safety assessments undertaken for the first 2 cycles will be as per the core protocol and module-specific Schedule of Activities (SoA). The safety run-in can comprise patients that are allocated to either the HER2 expression cohort (A.6.HER2e) or the HER2 mutation cohort (A.6.HER2m) to provide the earliest opportunity to assess tolerability of the combination in those approximately 6 patients.

After administration of the first dose to the first patient, at least 24 hours must be allowed before administration to the second patient in case of unexpected acute toxicity.

A patient will be evaluable for dose-limiting toxicity (DLT) safety assessment if they have received at least 75% of the scheduled dose. Any of the 6 patients who withdraw during the safety run-in can be replaced, except if they dose reduced or discontinued due to toxicity.

After the completion of 6 weeks (2 cycles) dosing in the first 6 evaluable patients in Module 6, all safety data (including, but not limited to, DLTs and adverse events of special interest (AESIs)), will be assessed to ensure the combination is safe and tolerable. This assessment, and subsequent go-ahead to continue dosing in the module, at a revised dose if indicated, will be undertaken by a Safety Review Committee (SRC).

Recruitment to Module 6 will be paused whilst the SRC convenes to assess the safety data at the end of the safety run-in phase. Additional patients may be dosed once this decision has been taken. If the combination dose is tolerated, patients from the safety run-in phase will contribute to the required enrolment total for the A.6.HER2e and A.6.HERm cohorts.

A separate SRC charter has been developed to elaborate on roles and responsibilities of SRC members, timing and purpose of SRC meetings.

The following DLT rules will be used in the safety run-in (6 evaluable patients):

- 0 to 1 patient with DLTs: continue recruitment
- ≥2 patients with DLTs: stop recruitment.

DLT is defined as any treatment-emergent adverse event (TEAE) not attributable to disease or disease-related processes that occurs during the DLT evaluation period (Day 1 to Day 42 in Cycles 1/2) and is Grade 3 or above according to National Cancer Institute Common Terminology Criteria for Adverse Event (NCI-CTCAE) version 4.03, with the exceptions as defined below. A comprehensive safety review of all safety data in the first 6 patients will be performed before

additional patients can be enrolled. This review will include all safety data from these 6 patients up until the sixth patient has completed 2 cycles of study treatment.

For haematological toxicities, a DLT is defined as follows:

- Grade 4 neutrophil count decreased lasting >7 days
- Febrile neutropenia
- Grade 4 anaemia
- Grade 4 platelet count decreased
- Grade 3 platelet count decreased lasting >7 days
- Grade 3 platelet count decreased with clinically significant haemorrhage
- Grade 4 lymphocyte count decreased lasting ≥14 days

For hepatic organ toxicities, a DLT is defined as follows:

- Grade 4 aspartate aminotransferase (AST) or alanine aminotransferase (ALT) increased
- AST or ALT ≥3 x upper limit of normal (ULN), if accompanied by Grade ≥2 blood bilirubin increased
- In patients without liver metastases, AST or ALT >5 x ULN lasting >3 days
- In patients with liver metastases, AST or ALT >5 x ULN lasting >3 days, if the baseline level was ≤3 x ULN
- In patients with liver metastases, AST or ALT >8 x ULN lasting >3 days, if the baseline level was >3 x ULN

For non-haematological, non-hepatic major organ toxicities, a DLT is defined as follows:

- Symptomatic congestive heart failure (CHF)
- Left ventricular ejection fraction (LVEF) decline to <40% or >20% drop from baseline
- Other Grade ≥3 non-haematological, non-hepatic major organ toxicities.

The following TEAEs are NOT considered DLTs:

- Grade 3 fatigue lasting <7 days
- Grade 3 nausea, vomiting, diarrhoea, or anorexia that has resolved to Grade ≤2 within 3 days
- Isolated laboratory findings not associated with signs or symptoms including Grade 3/4 alkaline phosphatase (ALP) increased, hyperuricemia, serum amylase increased, and lipase increased, and Grade 3 hyponatremia lasting <72 hours developed from Grade 1 at baseline
- Grade 3 lymphocyte count decreased.

If any of the above toxicities is observed during the DLT evaluation period, whether or not the toxicity is regarded as DLT will be determined based on consultation between the Investigator and Sponsor. In addition, with regard to other toxicities that hinder the conduct of the scheduled study treatment or anaemia with blood transfusion, whether or not they are regarded as DLT will be determined based on consultation between the Investigators and Sponsor.

4.2 Method of Assignment of Patients to Treatment Groups

Figure 3 in the core CSP is a schematic explaining the cohort naming convention. Figure 4 in the core CSP summarises the possible allocation cohorts stemming from the tumour molecular profile and treatment module. The tumour molecular profile (from pre-existing local data or prospective central laboratory tumour testing) is used to allocate patients to either a biomarker-matched treatment group (Group A) or a biomarker non-matched treatment group (Group B). Group C is a molecular aberration independent group.

Group A patients should have the qualifying/inclusion biomarker specific to the cohort and should not have any of the exclusion biomarkers. Initially, eligible patients in Group A will be enrolled *concurrently* into the biomarker-matched cohorts, except not all cohorts may be open for allocation at the same time.

Group B patients will be allocated according to whether they have primary resistance or acquired resistance to prior immunotherapy and should not have any of the exclusion biomarkers. The primary resistance and the acquired resistance are defined as follows:

Primary resistance: Patients who had anti-PD-1/PD-L1 containing therapy but had progression of disease (PD) within ≤24 weeks from the start of that treatment.
Acquired resistance: Patients with progressive disease >24 weeks from the start of anti-PD-1/PD-L1 containing therapy whilst still on that treatment.

This will be based on the time to progression on prior anti-PD-1/PD-L1 containing therapy. Enrolment to the biomarker non-matched cohorts will be *sequential* in module number order, such that once enrolment to the first primary (B.1.PRI) or acquired resistant (B.1.ACQ) cohort is complete, patients will be enrolled to a subsequent primary or acquired resistant cohort. The sequential order of the biomarker non-matched cohorts may be different between sites. In the event that the 'next' sequential module has not yet been approved in all countries, those countries where the next module has been approved may be allowed to enroll patients in the next module to enable the current module to be completed in countries where the next module has not yet been approved.

Group C was added to protocol version 10.0. Patient allocation to Group C will be independent of molecular aberration status.

Module 10 patients will be randomly allocated in a 2:1 ratio to receive 1 of the following 2 doses of AZD6738 in combination with durvalumab:

- AZD6738 160 mg BD
- AZD6738 240 mg BD

Module 10 patients will be stratified by prior response to immunotherapy; primary resistance or acquired resistance, as described above for Group B, before being randomly allocated to a cohort defined by the AZD6738 dose.

4.3 Determination of Sample Size

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

The primary efficacy endpoint is ORR (see Section 6.4.2). This endpoint is used to define the sample size. ORR is a well-established endpoint in early oncology studies and has been well reported in the literature for second-line NSCLC patients.

Per protocol version 9.0, approximately [redacted] evaluable patients will be in each treatment cohort, with the option for possible expansion should an efficacy signal be observed, such as 4 or more confirmed objective responses (complete response (CR), partial response (PR)). This may be to expand the size of a cohort to include approximately an additional 20 patients. Alternatively, patients could be enrolled to a non-comparative randomised expansion where approximately an additional [redacted] patients could be randomised to either study treatment or standard-of-care/treatment-of-physician's choice (to be determined and defined in the resulting amendment).

An analysis will be carried out after approximately the [redacted] evaluable patient in a cohort, or the final patient dosed in a cohort if enrolment has ended early, has had the opportunity for 2 on-treatment RECIST assessments or has discontinued or withdrawn from study treatment. The analysis will provide tolerability and safety data and will also give a reasonable chance of detecting any efficacy signal in this cohort, should one exist.

If the true ORR is equal to [redacted] then there is a [redacted] probability to see [redacted] out of [redacted] patients. Also, there is only a [redacted] to see [redacted] out of 20 patients, if the true ORR is [redacted].

Confidence intervals (Clopper-Pearson), will be constructed around the response rate observed in a cohort to enable decisions to be made around the likely success of future studies.

For example, with [redacted] patients, if the following response rates were observed, the [redacted] confidence interval (CI) around those response rates would be:

[redacted]

CCI [redacted]

In particular, there is CCI [redacted] confidence that the true response rate would be between CCI [redacted] if CCI [redacted] out of C [redacted] patients were observed.

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

CCI [redacted]

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

Molecular aberration independent cohorts (Group C)

CCI [redacted]

5 CHANGES IN PLANNED ANALYSES

5.1 Changes in the conduct of the study

Not applicable.

5.2 Changes from the analyses planned from the protocol

Any change to the planned analyses from the protocol will be listed in this section. Within each subsection, all the changes between the SAP and the CSP versions mentioned in the title will be provided. Changes are not cumulative from one subsection to another.

5.2.1 Changes within SAP v4.0 (01 April 2021, used for the modules 2 and 4 CSR) from CSP v6.0 (05 November 2019)

- CSP Section 6.4.1.3 Table 4 Overall Visit Response: Add rows for cases with target lesion at baseline not applicable.
- CSP Section 8.2.3 of Appendix O: Patients will record their blood pressure (BP) data using handheld electronic devices, to be provided by the study Sponsor. However, the BP device

used to record these additional measurements will also record the pulse rate. Hence pulse rate will also be measured along the BP measurements.

- CSP Section 8.5.3 Table 10 ADA blood sample schedule for durvalumab and trastuzumab deruxtecan: Pre-dose durvalumab for Module 5 was inadvertently removed.
- CSP Section 9.3 Populations for analyses. This section is slightly updated in the SAP for further clarity.
- CSP Section 9.4.1: CCI [redacted]
- CSP Section 9.4.1: Censoring for progression-free survival. Protocol states if the patient has no evaluable visits or does not have pre-dose data, they will be censored at 0 days unless they die within 2 visits of pre-dose. There is change in terminology for '0 days' which will be interpreted as 'Day 1' in the rest of the SAP document.
- CSP Section 9.4.1: Progression-Free Survival. If the patient progresses or dies after two or more missed visits, the patient will be censored at the time of the latest evaluable RECIST assessment prior to the two missed visits.
- CSP Section 9.4.2: General considerations. This section states that for each biomarker-matched cohort, the efficacy endpoints will be summarised for all patients and by their central test result. However, in certain circumstances and as described further down in Section 6.3.2, local test results might be used.
- CSP Section 9.4.2: General considerations. This section states that demographic data will be summarised on the safety population set. However, demographics data will be summarised using Intention-to-Treat (ITT) analysis set.
- CSP Section 9.4.4 states that total exposure (date of last dose minus date of first dose+1) and total time on study (date of discontinuation minus date of first dose+1) will be summarised. Total exposure calculation is referred to as total treatment duration, and the definition of total exposure duration per module are clarified in Section 6.5.1 and total time on study is not calculated and will not be reported as part of the study.
- CSP Section 9.4.5.2:
  - For the interim analysis, along with CCI [redacted] for each module stratified by cohort will be provided.
  - The duration of response section states Kaplan-Meier plots of DoR in the responding patients will be produced and appropriate descriptive summary statistics for DoR will be presented (n, number of responses that have progressed, median, quartile, minimum and maximum DoR). However, the minimum and maximum DoR will not be presented.

- CSP Section 9.4.6 safety analyses states that for re-allocated patients, TEAEs are defined as follows:
  - TEAE for first cohort is defined as from first dose of first cohort study drug up to 90 days following first cohort study drug discontinuation or until the day prior to first dose of second cohort study drug
  - TEAE for second cohort is defined as from first dose of second cohort study drug up to 90 days following second cohort study drug discontinuation. These data will be listed only.

  This is updated as follows:

  - For patients not re-allocated to a second HUDSON treatment cohort: A TEAE is defined as an event with an onset date or worsening in CTCAE grade on or after the date of first dose of any study drug and up to and including 90 days following the date of last dose of study drug.
  - For patients re-allocated to a second HUDSON treatment cohort: TEAE is defined any AE that started or worsened in CTCAE grade on or after the first dose of any study drug from the first cohort, until 90 days follow-up after discontinuation of study drug from the first cohort, unless the investigator assessed the relatedness of the AE with onset during this interval to the non-durvalumab study drug from the second cohort.
- CSP Section 9.4.7.2 CCI [redacted]
- CSP Section 9.4.7.3 CCI [redacted]

5.2.2 Changes within SAP v5.0 (09 November 2021) from CSP v9.0 (14 May 2021)

- CSP Section 3: CCI [redacted]
- CSP Section 8.2.1: Fibrinogen is listed as coagulation in SAP rather than haematology parameter in CSP.

- CSP Section 9.3: Populations for analyses. This section is slightly updated in the SAP for further clarity. There is also a change in definition of the Enrolled Subjects analysis set.
- CSP Section 9.4.1: CCI [redacted]
- CSP Section 9.4.1: Progression-Free Survival. If the patient progresses or dies after two or more missed visits, the patient will be censored at the time of the latest evaluable RECIST assessment prior to the two missed visits.
- CSP Section 9.4.2: In general, data relating to the re-allocation to a second cohort will be listed only with limited summary tables including re-allocated subjects' safety data, whereas CSP has a general statement that re-allocated subjects' safety data in the new cohort will be summarised
- CSP Section 9.4.2: General considerations. This section states that demographic data will be summarised on the safety population set. However, demographics data will be summarised using Intention-to-Treat (ITT) analysis set.
- CSP Section 9.4.5.2: For the interim analysis, along with CCI [redacted] for each module stratified by cohort will be provided.
- CSP Section 9.4.6: safety analyses states that for re-allocated patients, TEAEs are defined as follows:

  For patients not re-allocated to a second HUDSON treatment cohort:
  - TEAE is defined as any AE that started or worsened in CTCAE grade on or after the first dose of any study drug until 90 days follow-up after discontinuation of study drug.

  For patients re-allocated to a second HUDSON treatment cohort:
  - TEAE is defined as any AE that started or worsened in CTCAE grade on or after the first dose of any study drug from first cohort, until 90 days follow-up after discontinuation of study drug from first cohort, unless the investigator assesses the relatedness of the AE to "Other Study Treatment".
  - For the re-allocated patients, only AEs occurring in the first cohort will be considered for summaries/listings. AEs occurring in the second cohort will be flagged in the datasets and in general, presented in listings only. Deaths of re-allocated subjects will be included in the summary tables relating to all deaths observed during the module.

  This is updated as follows:

  - For patients not re-allocated to a second HUDSON treatment cohort: A TEAE is defined as an event with an onset date or worsening in CTCAE grade on or

after the date of first dose of any study drug and up to and including 90 days following the date of last dose of study drug.

- For patients re-allocated to a second HUDSON treatment cohort: TEAE is defined any AE that started or worsened in CTCAE grade on or after the first dose of any study drug from the first cohort, until 90 days follow-up after discontinuation of study drug from the first cohort, unless the investigator assessed the relatedness of the AE with onset during this interval to the non-durvalumab study drug from the second cohort.
- CSP Section 9.4.6: SAP clarifies text 'Any AE occurring within the defined 90-day follow-up period after discontinuation of study drug will be included in the AE summaries. AEs occurring after the 90-day follow-up period after discontinuation of study drug will be listed separately, but not included in the summaries.'

5.2.3 Changes from SAP v6.0 (07 July 2022) from the CSP v10.0 (12 April 2022)

- CSP Section 8.2.1: Fibrinogen is listed as coagulation in SAP rather than haematology parameter in CSP.
- CSP Section 9.3: Populations for analyses. SAP Table 12 includes a new footnote which clarifies how analysis sets are defined when presenting data following re-allocation, for re-allocated patients.
- CSP Section 9.4.1: Progression-Free Survival. If the patient progresses or dies after two or more missed visits, the patient will be censored at the time of the latest evaluable RECIST assessment prior to the two missed visits.
- CSP Section 9.4.6: AEs occurring in the second cohort will be flagged in the datasets and presented in listings only.

5.2.4 Changes from SAP v7.0 (07 February 2023) from the CSP v11.0 (16 August 2022)

- CSP Section Methods for statistical analysis: the section mention for non-matched cohort, efficacy endpoints will be summarised by actual resistance, but the resistance assigned by the investigator will be used.
- CSP Section 8.2.1: Fibrinogen is listed as coagulation in SAP rather than haematology parameter in CSP.

- CSP Section 9.5: for module 10, the first IA with approximately 16 patients in the 160 mg treatment cohort and approximately 8 patients in the 240 mg treatment cohort have completed 2 cycles of treatment has been removed from this SAP version.

5.2.5 Change from this current SAP version from the CSP v12.0 (1 March 2023)

- CSP Section Methods for statistical analysis: the section mention for non-matched cohort, efficacy endpoints will be summarised by actual resistance, but the resistance assigned by the investigator will be used.
- CSP Section 8.2.1: Fibrinogen is listed as coagulation in SAP rather than haematology parameter in CSP.
- CSP Section 9.5: the time to progression efficacy endpoint listed in the CSP for module 11 interim analysis is no longer planned to be analysed.

5.2.6 Changes in this current SAP version compared to CSP v13.0 (14 December 2023)

- In CSP Section 8.2.1 fibrinogen is listed as a haematology laboratory parameter, but in SAP Section 6.5.3 fibrinogen is listed as a coagulation laboratory parameter.
- In CSP Section 9.4.2 it mentions that the safety data for ongoing patients following the data cut-off for the modular CSR will be listed in a modular CSR addendum or final study CSR. These analyses have been removed from this SAP.
- In CSP Section 9.4.5.3 it mentions that screen failure OS analyses will be performed by biomarker status where available. These screen failure OS analyses by biomarker status have been removed from this SAP.

Sponsor:	AstraZeneca	Protocol/CIP Number:	D6185C00001/Multiple drugs
CIL Project Number:	40773		

6 BASELINE, EFFICACY AND SAFETY EVALUATIONS

6.1 Schedule of Activities

The SoA for pre-screening and screening visits, on-treatment visits for each treatment module and the optional re-allocated second on-treatment period is described in detail in CSP version 13.0 and respective appendices.

6.2 Time Point Algorithms

6.2.1 Study Day for First Study Treatment Allocation

The date of first dose of study medication will be considered as study day 1, and the day before the first dose of study medication will be study day -1. Study day will be calculated as:

- For days on or after first dose of study medication: Date of efficacy or safety assessment – Date of first dose of any study drug + 1
- For days prior to the first dose of study medication: Date of efficacy or safety assessment – Date of first dose of any study drug

For Modules 2, 3 and 10, there is a 7-day lead-in period (Cycle 0) of monotherapy with AZD9150 (module 2) and AZD6738 (modules 3 and 10). For these modules with a monotherapy lead-in period: study day 1 corresponds to Cycle 0 Day 1. For modules without a lead-in period: study day 1 corresponds to Cycle 1 Day 1. Study days will be calculated only for complete assessment dates (i.e., partial dates will have missing study day).

6.2.2 Definition of Study Day for re-allocated patients

For patients in Modules 1 to 5 re-allocated to a subsequent treatment module, study day relating to data collected during the subsequent treatment module will be calculated such that the date of first dose of the second treatment on HUDSON will be considered study day 1:

- For days on or after first dose of second medication: Date of assessment in second on-treatment period – Date of first dose of any study drug in second on-treatment period +1
- For days prior to the first dose of second medication: Date of assessment in second on-treatment period – Date of first dose of any study drug in second on-treatment period

Re-allocation will be restricted to Modules 1 to 5 and will not be offered from Module 6 onwards. From implementation of protocol version 10.0, re-allocation of patients to a different treatment cohort is no longer applicable.

6.2.3 Visit Windows

Analysis visit windows for safety variables will be based on scheduled visits of the SoA for each treatment module with the exception of the additional blood pressure measurements for Module 7. The handling of these additional blood pressure measurements will be described in Section 6.5.4.1.2. The baseline safety window ranges from the date of main screening visit to date of first dose of any study drug.

For all modules except Module 6, analysis visit windows for tumour assessment efficacy variables will be based on post baseline scans scheduled every 6 weeks for the first 24 weeks relative to Cycle 1 Day 1, and every 8 weeks thereafter until disease progression. For Module 6, post baseline scans are scheduled every 6 weeks for the first 24 weeks relative to the date of first dose (Cycle 1 Day 1), then every 9 weeks thereafter until disease progression.

Baseline scans are to be performed no more than 28 days before the first dose of any study drug.

Generally, the window for the visits following start of first dose of any study drug will be constructed such that the upper limit of the interval falls halfway between the two visits. If a patient has more than 1 assessment occurring in the same visit window, the data from the visit closest to the scheduled study day will be used. If two visits on different dates have the same distance from the scheduled study day, the data of the visit before the scheduled study day will be used. If there are multiple assessments on the selected study day then for quantitative variables the mean value, and for qualitative variables the worst value (or best value, if selected for baseline), will be used. Additional details for baseline visit windows are described in Section 6.3.1.

6.2.4 Analysis Period

The following 2 analysis periods for adverse events will be defined:

- On-treatment period: defined as the period between first dose of any study medication to the last dose of study medication (inclusive).
- Safety follow-up period: defined as the period from last dose of any study medication +1 day to last dose of study medication + 90 days (inclusive).

An additional period will be used only for selected summaries of patient deaths after the end of the safety follow-up period and prior to the DCO.

6.3 Baseline Assessments

6.3.1 Baseline Value

For safety and efficacy variables, baseline will be the last non-missing value obtained prior to the first dose of any study drug. Any information taken on and after time of first dose will be regarded as post baseline information.

For tumour assessment, the baseline assessment should be performed no more than 28 days before the first dose of any study drug, or else the baseline tumour assessment will be missing. However, depending on the patient's clinical history and the time from baseline assessment to first dose of any study drug, baseline tumour assessments recorded out of visit window could be exceptionally used in the analysis if no other data is available for baseline. A RECIST scan performed up to but not including 35 days prior to first dose of study drug will be used. Any RECIST scan performed between 35 and 42 days prior to first dose would require AstraZeneca input. Any RECIST scan performed more than 42 days prior to first dose should not be used.

If two visits are equally eligible to assess patient status at baseline (e.g., screening and baseline assessments both on the same date prior to first dose/administration with no washout or other intervention in the screening period), the average should be taken as the baseline value. In the scenario where there are two assessments on the same day, one with time recorded and the other without time recorded, the one with time recorded would be selected as baseline. If no value exists before the first dose of any study drug, then the baseline value will be treated as missing.

The mean of the screening and Day 1 pre-dose assessment of the vital signs assessments will be used as the baseline for the reporting for all vital signs measurements performed at the study site, including the additional vital signs measurements performed at home by the patient for Module 7.

6.3.2 Allocation of Patients to Cohorts

The study is modular in design, i.e., there are multiple modules in the study. Within each module, there will be treatment cohorts. The cancer biomarker testing is used to stratify and allocate patients into the multiple treatment arms of the study. Allocation to a treatment cohort will be guided by analysis of tumour biomarker profile to a biomarker-matched cohort (Group A), a biomarker non-matched cohort (Group B) or a molecular aberration independent cohort (Group C). Within Group B (biomarker non-matched), the cohorts will be stratified into patients who had primary resistance or developed acquired resistance while on immunotherapy. Module 10 patients will be stratified on their resistance type, before being randomly allocated (in a 2:1 ratio to Cohort C.10.160 or Cohort C.10.240) to a treatment cohort defined by the AZD6738 BD dose patients will receive. Module 11 patients will be summarized on their resistance type.

There are multiple routes for patient allocation in the study, and the diagnostic tumour sample journey is described in the HUDSON Pathology and Genomic Testing Manual.

The confirmation of patient allocation to a biomarker matched cohort will focus on detection of qualifying biomarkers specific to the cohort and none of the exclusion biomarkers. The confirmation of patient allocation to a biomarker non-matched cohort will focus on the detection of any exclusion biomarkers.

Further details on the qualifying and exclusion biomarkers can be found in the HUDSON Pathology and Genomic Testing Manual.

6.3.2.1 Analysis Classification of Patients to Biomarker Matched Cohort (Group A)

For the statistical analysis of some efficacy endpoints, patients will be classified into 1 of 4 categories of biomarker tests result:

- If the central laboratory test detects a qualifying biomarker specific to the cohort and does not detect any of the exclusion biomarkers, then these will be classified as 'Qualifying biomarker detected/Exclusion biomarker not detected'.
- If the central laboratory test detects a qualifying biomarker specific to the cohort and detects any of the exclusion biomarkers, then these will be classified as 'Qualifying biomarker detected/Exclusion biomarker detected'.
- If the central laboratory test does not detect a qualifying biomarker specific to the cohort, then these will be classified as 'Qualifying biomarker not detected'.
- If the central laboratory testing fails or is not performed, then these will be classified as 'Unknown' for the whole test sample, i.e., unknown result for all biomarkers.
- If there are multiple results for a test from central laboratories, then the results that detect Qualifying biomarkers and those that detect Exclusion biomarkers will be considered for classification.

  For example, if there are any Qualifying biomarker results of 'detected', then these will be classified as 'Qualifying biomarker detected' (even if other results report not detected or unknown/missing). If there are Exclusion biomarker results of 'Detected', then these will be classified as 'Exclusion biomarker detected' (even if other results report not detected or unknown/missing). If there are Exclusion biomarker results of 'Not detected', then these will be classified as 'Exclusion biomarker not detected' (even if other results report unknown/missing).

In addition, where the results from the central laboratories are unknown/missing, the results from the local laboratories will be used.

- For the patients enrolled under protocol version 3.1 and above, the local test results will be used only if they are based on a local AstraZeneca approved test.

- For the patients enrolled prior to the protocol version 3.1, the local test results will be used without ascertaining whether they are AstraZeneca approved test or not.
- When the local test results are detected/not detected, then these results will be considered as detected/not detected as applicable instead of the unknown/missing results from the central laboratory data.

  A specific rule will apply to EGFR. The central laboratories will test EGFR mutations while the local laboratories will test for eight other EGFR alterations. The following rules will apply:
  - If at least one of the EGFR alterations is detected, then the results will be considered as detected.
  - If at least one of the EGFR alterations is unknown and the other alterations are not detected, then the results will be considered as unknown.
  - If all the EGFR alterations are not detected, then the results will be considered as not detected.
- If there are multiple results for a test, then the results that detect Qualifying biomarkers and those that detect Exclusion biomarkers will be considered for classification.

  For example, if there are any Qualifying biomarker results of 'detected', then these will be classified as 'Qualifying biomarker detected' (even if other results report not detected or unknown/missing). If there are Exclusion biomarker results of 'Detected', then these will be classified as 'Exclusion biomarker detected' (even if other results report not detected or unknown/missing).
- For the patients enrolled under protocol version 1, if the exclusion biomarkers EGFR, ROS1 and ALK are 'not detected' then these will be classified as 'Exclusion Biomarker not detected' (even if other results for EGFR, ROS1 and ALK report unknown/missing).
- For the patients enrolled under protocol v2 and above, if there are Exclusion biomarker results of 'Not detected' for EGFR and ALK, and 'Not detected' or 'Unknown' for ROS1, BRAF, MET or RET, then these will be classified as 'Exclusion biomarker not detected' (even if other results for EGFR and ALK report unknown/missing).
- If any of the exclusion biomarker tests listed for the protocol version 1 (EGFR, ROS1 and ALK) or for the protocol version 2 and above (EGFR, ALK) that patients have been enrolled to are 'unknown' and none of them was 'detected' then these will be classified as 'Exclusion biomarker unknown'. If one is detected, it will be classified as "Exclusion biomarker detected".

Any inconsistencies in the patient data qualifying biomarker (i.e., patient is dosed although qualifying biomarker is not 'Detected') will be discussed by AstraZeneca team members. If patient

classification updates are required for the purpose of the analysis, they will be managed by the means of an external file to be finalized prior to database lock (DBL).

6.3.2.2 Analysis Classification of Patients in Biomarker Non-Matched Cohort (Group B)

For the statistical analysis of some efficacy endpoints, patients will be classified into 2 categories of biomarker tests result:

- If the central laboratory test does not detect any of the exclusion biomarkers, then these will be classified as 'Exclusion biomarker not detected'.
- If the central laboratory test detects any of the exclusion biomarkers, then these will be classified as 'Exclusion biomarker detected'.
- If there are multiple results for a test from central laboratories, then the results that detect Exclusion biomarkers will be considered for classification.

  For example, if there are Exclusion biomarker results of "Detected", then these will be classified as 'Exclusion biomarker detected' (even if other results report not detected or unknown/missing). If there are Exclusion biomarker results of 'Not detected', then these will be classified as 'Exclusion biomarker not detected' (even if other results report unknown/missing).

In addition, where the results from the central laboratories are unknown/missing, the results from the local laboratories will be used:

- For the patients enrolled under protocol version 3.1 and above, the local test results will be used only if they are based on a local AstraZeneca approved test.
- For the patients enrolled prior to the protocol version 3.1, the local test results will be used without ascertaining whether they are AstraZeneca approved test or not.
- When the local test results are detected/not detected, then these results will be considered as detected/not detected as applicable instead of the unknown/missing results from the central laboratory data.

  A specific rule will apply to EGFR. The central laboratories will test EGFR mutations while the local laboratories will test for eight other EGFR alterations. The following rules will apply:
  - If at least one of the EGFR alterations is detected, then the results will be considered as detected.

- If at least one of the EGFR alterations is unknown and the other alterations are not detected, then the results will be considered as unknown.
- If all the EGFR alterations are not detected, then the results will be considered as not detected.

- If there are multiple results for a test from local laboratories, only the results that detect exclusion biomarkers will be considered for classification. For example, if there are Exclusion biomarker results of 'Detected', then these will be classified as 'Exclusion biomarker detected' (even if other results report not detected or unknown/missing). If there are Exclusion biomarker results of 'Not detected', then these will be classified as 'Exclusion biomarker not detected' (even if other results report unknown/missing).
- For the patients enrolled under protocol version 1, if the exclusion biomarkers EGFR, ROS1 and ALK are 'not detected' then these will be classified as 'Exclusion Biomarker not detected'.
- For the patients enrolled under protocol v2 and above, if all 6 exclusion biomarkers EGFR, ALK, ROS1, BRAF, MET and RET are 'not detected' then these will be classified as 'Exclusion Biomarker not detected'.
- If any of the exclusion biomarker tests listed for the protocol version 1 (EGFR, ROS1 and ALK) or for the protocol version 2 and above (EGFR, ALK, ROS1, BRAF, MET and RET) that patients have been enrolled to are 'unknown' and none of them is 'detected' then these will be classified as 'Exclusion biomarker unknown'. If at least one is detected, it will be classified as "Exclusion biomarker detected".

Any inconsistencies in the exclusion biomarker patient data (i.e. patient is dosed although exclusion biomarker is detected) will be discussed by AstraZeneca team members. If patient classification updates are required for the purpose of the analysis, they will be managed by the means of an external file to be finalized prior to DBL.

Note: In all the above cases, 'unknown' refers to 'No known result' i.e. no result of 'detected' or 'not detected'. This will include 'not done', or missing result, and thus the status on presence/absence of the biomarker is 'Unknown'.

6.4 Efficacy Variables

6.4.1 Evaluation Criteria and Response Categories using RECIST version 1.1

For all patients, the radiological tumour assessments will be used to determine each patient's visit response according to RECIST 1.1. The radiological tumour response assessments will also be used

to determine if and when a patient has progressed in accordance with standard RECIST 1.1 and also their best objective response to study treatment. As patients may be treated beyond progression, tumour response data may be used to determine each patient's visit response according to a modified version of RECIST 1.1. CCI [redacted] Note that the terms RECIST and RECIST 1.1 are used in this SAP, both refer to RECIST version 1.1.

Baseline radiological tumour assessments are to be performed no more than 28 days before the first dose of any study drug and ideally as close as possible to the first dose of any study drug (refer to Section 6.3.1 for more details). Tumour assessments are then performed every 6 weeks (±1 week) relative to the Cycle 1 Day 1 for the first 24 weeks, and every 8 weeks (±1 week) (every 9 weeks for Module 6) thereafter until objective disease progression where objective disease progression as defined by RECIST 1.1 and confirmed with a subsequent scan (in the absence of clinically significant deterioration). Per protocol, scheduled radiological scans will continue for patients with confirmed radiological disease progression and who, in the opinion of the investigator, are still receiving clinical benefit from continuing study treatment. These assessments will continue for as long as the patient is still receiving study treatment.

If an unscheduled assessment is performed, and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits. This schedule is to be followed in order to minimise any unintentional bias caused by some patients being assessed at a different frequency than other patients.

From the investigator's review of the imaging scans, the RECIST tumour response data will be used to determine each patient's visit response according to RECIST version 1.1. At each visit, patients will be programmatically assigned a visit response of CR, PR, stable disease (SD) or progressive disease (PD) according to RECIST 1.1, using the information from target lesions (TLs), non-target lesions (NTLs) CCI [redacted] and depending on the status of their disease compared with baseline and previous assessments. If a patient has had a tumour assessment which cannot be evaluated, then the patient will be assigned a visit response of not evaluable (NE) (unless there is evidence of progression in which case the response will be assigned as PD).

Please refer to Sections 6.4.1.1, 6.4.1.2 and 6.4.1.3 for definitions of target lesion, non-target lesion and overall visit responses respectively. RECIST outcomes (i.e., PFS, ORR etc.) will be calculated programmatically for the site investigator data from the overall visit responses.

6.4.1.1 Target Lesions Visit Response

Measurable disease is defined as having at least one measurable lesion, not previously irradiated (unless lesion has clearly progressed since irradiation) or biopsied per the protocol (unless no other lesions are suitable for biopsy), which is ≥ 10 mm in the longest diameter (LD) (except lymph nodes

which must have short axis ≥ 15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) and which is suitable for accurate repeated measurements. A patient can have a maximum of 5 measurable lesions recorded at baseline with a maximum of 2 lesions per organ (representative of all lesions involved and suitable for accurate repeated measurement) and these are referred to as target lesions (TLs). If more than one baseline scan is recorded, then measurements from the one that is closest and prior to the start of any study drug will be used to define the baseline sum of TLs.

All other lesions (or sites of disease) not recorded as TL should be identified as NTLs at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits.

Table 2: TL Visit Responses

Visit Reponses	Description
Complete response (CR)	Disappearance of all TLs since baseline. Any pathological lymph nodes selected as TLs must have a reduction in short axis to <10mm.
Partial response (PR)	At least a 30% decrease in the sum of diameters of TLs, taking as reference the baseline sum of diameters, as long as criteria for PD are not met.
Progressive disease (PD)	A ≥ 20% increase in the sum of diameters of TLs and an absolute increase of ≥ 5mm, taking as reference the smallest sum of diameters since treatment started including the baseline sum of diameters.
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD
Not evaluable (NE)	Only relevant if any of the TLs at follow-up were not assessed or not evaluable (e.g., missing anatomy) or had a lesion intervention at this visit; and scaling up could not be performed for lesions with interventions. Note: If the sum of diameters meets the PD criteria, PD overrides not evaluable as a TL response

Rounding of TL Data

For calculation of PD and PR, the percentage changes from baseline and previous minimum in sum of diameters should be rounded to 1 decimal place before assigning a TL response. For example, 19.95% should be rounded to 20.0% but 19.94% should be rounded to 19.9%.

Missing TL Data

If all TL measurements are missing then the TL visit response is not evaluable (NE). Overall visit response will also be NE, unless there is a progression of non-TLs [redacted], in which case the response will be PD.

Lymph Nodes

For lymph nodes, if the size reduces to < 10mm then these are considered non-pathological. However, a size will still be given and this size should still be used to determine the TL visit response as normal. In the special case where all lymph nodes are < 10mm and all other TLs are 0mm then although the sum may be >0mm the calculation of TL response should be over-written as a CR.

TL Visit Responses Subsequent to CR

A CR can only be followed by CR, PD or NE. If a CR has occurred, then the following rules at the subsequent visits must be applied:

Step 1: If all the TLs have disappeared and all TLs meet the CR criteria (i.e. 0mm or a short axis < 10mm for lymph nodes respectively) then response will be set to CR.

Step 2: If not all lesions meet the CR criteria (e.g. progression of one lesion) and the sum of lesions meets the criteria for PD then response will be set to PD.

Step 3: If after steps 1 and 2, a response can still not be determined, the response will be set to NE.

TL Too Big to Measure

If a TL becomes too big to measure this should be indicated in the database and a size ('x') above which it cannot be accurately measured should be recorded. If using a value of x in the calculation of TL response would not give an overall visit response of PD, then this will be flagged and reviewed by the study team. It is expected that a visit response of PD will remain in the vast majority of cases.

TL Too Small to Measure

If a TL becomes too small to measure, then this will be indicated as such on the case report form and a value of 5mm will be entered into the database and used in TL calculations. However, a smaller value may be used if the radiologist has not indicated 'too small to measure' on the case report form and has entered a smaller value that can be reliably measured. If a TL response of PD results, then this will be reviewed by the study team.

Irradiated Lesions/Lesion Intervention

In general, previously irradiated lesions (i.e. lesion irradiated prior to entry into the study) should be recorded as NTLs and should not form part of the TL assessment. However, a previously irradiated lesion can be included in the TL assessment if it has clearly progressed, as per the inclusion criterion 8. Any TL (including lymph nodes), which has had intervention during the study (for example, irradiation / palliative surgery / embolisation), should be handled in the following way and once a lesion has had intervention then it should be treated as having intervention for the remainder of the study noting that an intervention will most likely shrink the size of tumours. Note: Biopsies should not be included as an intervention unless in the Investigator's opinion there is a significant impact on the lesion size.

Step 1: The diameters of the TLs (including the lesions that have had intervention) will be summed and the calculation will be performed in the usual manner. If the visit response is PD this will remain as a valid response category.

Step 2: If there was no evidence of progression after step 1, treat the lesion diameter (for those lesions with intervention) as missing and if ≤ 1/3 of the TLs have missing measurements then scale up as described in the 'Scaling' section below. If the scaling results in a visit response of PD then the patient would be assigned a TL response of PD.

Step 3: After both steps, if PD has not been assigned, then if appropriate (i.e. if ≤ 1/3 of the TLs have missing measurements), the scaled sum of diameters calculated in step 2 should be used, and PR or SD then assigned as the visit response. Patients with intervention are evaluable for CR as long as all non-intervened lesions are 0 (or <10mm for lymph nodes) and the lesions that have been subject to intervention have a value of 0 (or <10mm for lymph nodes) recorded. If scaling up is not appropriate due to too few non-missing measurements, then the visit response will be set as NE.

At subsequent visits, the above steps will be repeated to determine the TL and overall visit response. When calculating the previous minimum, lesions with intervention should be treated as missing and scaled up (as per step 2 above).

Scaling

If > 1/3 of TL measurements are missing then TL response will be NE, unless the sum of diameters of non-missing TL would result in PD (i.e. if using a value of 0 for missing lesions, the sum of diameters has still increased by 20% or more compared to nadir and the sum of TLs has increased by ≥5mm from nadir).

If ≤ 1/3 of the TL measurements are missing, then the results will be scaled up (based on the sizes at the nadir visit to give an estimated sum of diameters) and this will be used in calculations; this is equivalent to comparing the visit sum of diameters of the non-missing lesions to the nadir sum of diameters excluding the lesions with missing measurements.

Example of Scaling

Lesion 5 is missing at a follow-up visit. The nadir TL sum including lesions 1-5 was 74 mm. The sum of lesions 1-4 at the follow-up is 68 mm. The sum of the corresponding lesions at the nadir is 62 mm.

Scale up as follows to give an estimated TL sum of 81 mm:

$$\frac{\begin{pmatrix}\text{Sum of lesions } 1-4\\ \text{at follow-up}\end{pmatrix} \times \begin{pmatrix}\text{Nadir TL sum}\\ \text{including lesions } 1-5\end{pmatrix}}{\begin{pmatrix}\text{Sum of corresponding}\\ \text{lesions at nadir}\end{pmatrix}} = \frac{68 \times 74}{62} = 81\ mm$$

CR will not be allowed as a TL response for visits where there is missing data. Only PR, SD or PD (or NE) could be assigned as the TL visit response in these cases. However, for visits with ≤1/3 lesion assessments not recorded, the scaled-up sum of TLs diameters will be included when defining the nadir value for the assessment of progression.

Lesions that Split in Two

If a TL splits in two, then the LDs of the split lesions should be summed and reported as the LD for the lesion that split.

Lesions that Merge

If two TLs merge, then the LD of the merged lesion should be recorded for one of the TL sizes and the other TL size should be recorded as 0cm.

Change in Method of Assessment of TLs

In this study, the TLs will be assessed using CT or MRI. If a change in method of assessment occurs between CT and MRI this will be considered acceptable and no adjustment within the programming is needed.

6.4.1.2 Non-Target Lesions [redacted] – site investigator data

At each visit, the investigator should record an overall assessment of the NTL response. This section provides the definitions of the criteria used to determine and record overall response for NTL at the investigational site at each visit.

NTL response will be derived based on the Investigator's overall assessment of NTLs as follows:

Table 3: NTL Visit Responses

Visit Responses	Description
Complete Response (CR)	Disappearance of all NTLs present at baseline with all lymph nodes non-pathological in size (<10 mm short axis).
Progressive Disease (PD)	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
Non-CR/Non-PD	Persistence of one or more NTLs with no evidence of progression.
Not Evaluable (NE)	Only relevant when one or some of the NTLs were not assessed and, in the investigator's opinion, they are not able to provide an evaluable overall NTL assessment at this visit.
Not Applicable (NA)	Only relevant if there are no NTLs at baseline.

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 the presence of SD or PR in TLs, the overall tumour burden has increased sufficiently to merit a determination of disease progression. A modest 'increase' in the size of one or more NTLs is usually not sufficient to qualify for unequivocal progression status.

CCI

[redacted]

Patients with 'symptomatic progression' requiring discontinuation of treatment without objective evidence of disease progression at that time should continue to undergo tumour assessments where possible until objective disease progression is observed.

6.4.1.3 Overall Visit Response

Table 4 defines how the previously defined programmatically derived TL visit response and investigator NTL visit response [redacted] to give an overall visit response.

Table 4: Overall Visit Responses

Target visit response (programmatically derived)	Non-Target visit response (investigator)	[redacted]	Overall Visit Response (programmatically derived)
CR	CR or NA		**CR**
CR	Non-CR/Non-PD or NE		**PR**
PR	CR, Non-CR/Non-PD, NE or NA		**PR**
SD	CR, Non-CR/Non-PD, NE or NA		**SD**
PD	Any		**PD**
Any	PD		**PD**
Any	Any		**PD**
NE	CR, Non-CR/Non-PD or NE or NA		**NE**
NA	CR		**CR**
NA	Non-CR/Non-PD		**SD**
NA	NE		**NE**

NA: Not applicable (only relevant if there were no target lesion or non-target lesions at baseline). NE: Not Evaluable

6.4.2 Primary Efficacy Variable

6.4.2.1 Best objective response

Best objective response will be provided as a supportive endpoint for primary efficacy variable-ORR.

Best objective response (BoR) is calculated based on the overall visit responses from each RECIST assessment, described in Section 6.4.1.3. It is the best response a patient has had following first dose of any study drug but prior to starting any subsequent cancer therapy (including any subsequent HUDSON study treatment) and up to and including RECIST progression (unconfirmed or subsequently confirmed) or the last evaluable assessment in the absence of RECIST progression. Categorisation of BoR will be based on RECIST 1.1 using the following response categories: CR, PR, SD, PD and NE.

CR or PR must be confirmed. For determination of a best response of SD, the earliest of the dates contributing towards a particular overall visit assessment will be used. For all modules except Modules 2, 3 and 10, SD should be recorded at least 6 weeks minus 1 week, i.e. 35 days (to allow for an early assessment within the assessment window of 1 week), after first dose/administration of study medication. For Modules 2, 3 and 10, there is a 7-day lead-in period. Thus, SD should be recorded at least 7 weeks minus 9 days, i.e. 40 days (to allow for an early assessment within the assessment window of 1 week + 2 days for Cycle 1 Day 1 assessment window), after first dose/administration of study medication. For CR/PR, the initial overall visit assessment which showed a response will use the latest of the dates contributing towards a particular overall visit assessment.

BoR will be determined programmatically based on RECIST using all site investigator data up until the first progression event. The denominator will be consistent with that used in the ORR analysis.

For patients whose progression event is death, BoR will be calculated based upon all evaluable RECIST assessments prior to death.

For all modules except Modules 2, 3 and 10, if a patient dies with no evaluable RECIST assessments, and if the death occurs ≤13 weeks (i.e. 12 weeks + 1 week to allow for a late assessment within the assessment window) after first dose/administration of study medication, then BoR will be assigned to the PD category. For patients who die with no evaluable RECIST assessments, if the death occurs >13 weeks after start of any study drug then BoR will be assigned to the NE category.

For Modules 2, 3 and 10, if a patient dies with no evaluable RECIST assessments, and if the death occurs ≤ 100 days (i.e. 12 weeks + 1 week of lead-in cycle + 1 week to allow for a late assessment within the assessment window + 2 days of Cycle 1 Day 1 assessment window) after first dose/administration of study medication, then BoR will be assigned to the PD category. For patients

who die with no evaluable RECIST assessments, if the death occurs >100 days after start of any study drug then BoR will be assigned to the NE category.

A patient will be classified as a responder if the RECIST criteria for a CR or PR are satisfied at any time following first dose/administration of study medication, prior to RECIST progression and prior to starting any subsequent cancer therapy (including any subsequent HUDSON study treatment). All responses of CR or PR must be confirmed.

6.4.2.2 Objective response rate

The primary efficacy endpoint of this study is the ORR, where ORR is defined as the percentage of patients with a confirmed investigator-assessed response of CR or PR.

A confirmed response of CR/PR means that a response of CR/PR is recorded at 1 visit and confirmed by repeat imaging not less than 4 weeks after the visit when the response was first observed with no evidence of progression between the initial and CR/PR confirmation visit. Data obtained up until progression, or last evaluable assessment in the absence of progression, will be included in the assessment of ORR. Patients who discontinue study drug without progression, receive a subsequent anti-cancer therapy (note that for this analysis, radiotherapy is not considered a subsequent anti-cancer therapy), including any subsequent HUDSON study treatment, and then respond will not be included as responders in the ORR (i.e. both visits contributing to a response must be prior to subsequent therapy for the patient to be considered as a responder).

In the case where a patient has two non-consecutive visit responses of PR, then, as long as the time between the 2 visits of PR is greater than 4 weeks and there is no PD between the PR visits, the patient will be defined as a responder. Similarly, if a patient has visit responses of CR, NE, CR, then, as long as the time between the 2 visits of CR is greater than 4 weeks, then a best response of CR will be assigned.

6.4.3 Secondary Efficacy Variables

6.4.3.1 Overall Survival

Overall survival (OS) is defined as the time from the first dose of any study drug until death due to any cause regardless of whether the patient withdraws from study treatment or receives subsequent cancer therapy (i.e. date of death or censoring – date of first dose + 1). 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 (SUR_DAT, recorded within the SUR module of the electronic case report form (eCRF)).

Note: Survival calls will be made in the week following the date of data cut-off (DCO) for the analysis, and if patients are confirmed to be alive or if the death date is post the DCO date these patients will be censored at the date of DCO. The status of ongoing, withdrawn (from the study) and "lost to follow-up" patients at the time of the final OS analysis should be obtained by the site

personnel by checking the patient's notes, hospital records, contacting the patient's general practitioner and checking publicly-available death registries. In the event that the patient has actively withdrawn consent to the processing of their personal data, the vital status of the patient can be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws.

Note that for any OS analysis performed prior to the final OS analysis, in the absence of survival calls being made, it may be necessary to use all relevant CRF fields to determine the last recorded date on which the patient was known to be alive for those patients still on treatment (since the SUR module is only completed for patients off treatment if a survival sweep is not performed). The last date for each individual patient is defined as the latest among the dates recorded on the case report forms (CRFs) but not limited to the following:

- AE start and stop dates
- Admission and discharge dates of hospitalization
- Study treatment date
- End of treatment date
- Laboratory test dates
- Date of vital signs
- Disease assessment dates on RECIST CRF
- Start and stop dates of subsequent anticancer treatment
- Date last known alive on survival status CRF
- End of study date
- Pre-screening informed consent date
- Main screening informed consent date
- Concomitant procedures
- Consent withdrawal

In case the death date of a patient is partially recorded (see Section 7.3.3) then the patient will be censored at the imputed date if it is the latest date among those recorded in the CRFs.

6.4.3.2 Disease Control Rate

6.4.3.2.1 All Modules except Modules 2, 3 and 10

Disease control rate (DCR) at 12 weeks is defined as the percentage of patients who have BoR of CR or PR in **the first 13 weeks** after the start of any study drug (to allow for a late assessment

within the assessment window), or with duration of SD for **at least 11 weeks** after the start of any study drug (to allow for an early assessment within the assessment window) where duration of SD is calculated as per Section 6.4.3.2.3.

Disease control rate (DCR) at 24 weeks is defined as the percentage of patients who have BoR of CR or PR **in the first 25 weeks** after the start of any study drug (to allow for a late assessment within the assessment window), or with duration of SD for **at least 23 weeks** after the start of any study drug (to allow for an early assessment within the assessment window) where duration of SD is calculated as per Section 6.4.3.2.3.

6.4.3.2.2 Modules 2, 3 and 10

For Module 2, there is lead-in period of 7 days, i.e. one week.

Disease control rate (DCR) at 12 weeks is defined as the percentage of patients who have BoR of CR or PR in **the first 100 days (13 weeks + 1 week of lead-in period + 2 days of Cycle 1 Day 1 visit window)** after the start of any study drug (to allow for a late assessment of within the assessment window + 2 days for Cycle 1 Day 1 assessment window), or with duration of SD for **at least 86 days (11 weeks + 1 week of lead-in period + 2 days of Cycle 1 Day 1 visit window)** after the start of any study drug (to allow for an early assessment within the assessment window) where duration of SD is calculated as per Section 6.4.3.2.3.

Disease control rate (DCR) at 24 weeks is defined as the percentage of patients who have BoR of CR or PR **in the first 184 days (25 weeks + 1 week of lead-in period + 2 days)** after the start of any study drug (to allow for a late assessment within the assessment window + 2 days for Cycle 1 Day 1 assessment window), or with duration of SD for **at least 170 days (23 weeks + 1 week of lead-in period + 2 days of Cycle 1 Day 1 visit window)** after the start of any study drug (to allow for an early assessment within the assessment window) where duration of SD is calculated as per Section 6.4.3.2.3.

For modules 3 and 10, there is also a lead-in period of 7 days, i.e. one week, a different approach is used.

Disease control rate (DCR) at 12 weeks is defined as the percentage of patients who have BoR of CR or PR in **the first 100 days (13 weeks + 1 week of lead-in period + 2 days of Cycle 1 Day 1 visit window)** after the start of any study drug (to allow for a late assessment within the assessment window + 2 days for Cycle 1 Day 1 assessment window), or with duration of SD for **at least 82 days (11 weeks + 1 week of lead-in period - 2 days of Cycle 1 Day 1 visit window)** after the start of any study drug where duration of SD is calculated as per Section 6.4.3.2.3

Disease control rate (DCR) at 24 weeks is defined as the percentage of patients who have BoR of CR or PR **in the first 184 days (25 weeks + 1 week of lead-in period + 2 days)** after the start of

any study drug (to allow for a late assessment within the assessment window + 2 days for Cycle 1 Day 1 assessment window), or with duration of SD for **at least 166 days (23 weeks + 1 week of lead-in period - 2 days of Cycle 1 Day 1 visit window)** after the start of any study drug where duration of SD is calculated as per Section 6.4.3.2.3

6.4.3.2.3 CCI [redacted] CCI [redacted] is defined as the time from first dose of study drug until CCI [redacted] whichever occurs first:

CCI [redacted]

[redacted] after the start of subsequent cancer therapy should not be included in this duration. Censoring rules will follow those defined for progression-free survival in Section 6.4.3.5.

6.4.3.3 Best Percentage Change from Baseline in Tumour Size

The best percentage change in tumour size from baseline will be reported, i.e. the maximum reduction from baseline or the minimum increase from baseline in the absence of a reduction from baseline based on all post baseline assessments. Only assessments performed before patients receive a subsequent anti-cancer therapy, including any subsequent HUDSON study treatment, will be included in the calculation of best percentage change.

Tumour size is the sum of the longest diameters (or short axis measurements for lymph nodes) of the target lesions. Target lesions are measurable tumour lesions. Baseline for RECIST is defined to be the last evaluable assessment prior to starting treatment. The percentage change in target lesion tumour size at each week x for which data are available will be obtained for each patient taking the difference between the sum of the target lesions at each week x and the sum of the target lesions at baseline divided by the sum of the target lesions at baseline multiplied by 100 (i.e. (week x - baseline)/baseline * 100).

Only patients with measurable disease at baseline should be included in summaries of best percentage change in tumour size (measurable disease is as denoted on the CRF by the investigator assessment). If, after the scaling up rules have been applied, best percentage change cannot be calculated due to missing data, a patient has no post baseline assessments, then the following imputation rules should be applied:

a) If there is no observed TL tumour size measurement data post-progression (unconfirmed or subsequently confirmed) but there is evidence of disease progression for the individual during their time on study, where evidence of progression is defined as unequivocal progression of NTLs, CCI [redacted] as determined by an investigator (i.e. investigator's

opinion of response recorded on the RECIST eCRF is PD at that assessment or study treatment was discontinued for progression in the assessment time window), and there are at least 5 patients within that cohort with non-missing TL tumour size who have also progressed then impute a best percentage change from baseline as the median best percentage change from patients with non-missing TL tumour size who also have progressed. However, if there are less than 5 patients within that cohort with non-missing TL tumour size who have also progressed then impute a best percentage change from baseline as 20%.

b) If there is no evidence of progression, it will be assumed that the data is missing completely at random; and the patient will be excluded from the analysis.

c) If it is known that the patient has died, a best percentage change from baseline will be imputed as the maximum (i.e. corresponding to the biggest increase in TL tumour size) best percentage change reported on the study for each module.

6.4.3.4 Duration of Response

Duration of response will be defined as the time from the date of first documented response (which is subsequently confirmed) until date of documented progression or death in the absence of disease progression (i.e., date of PFS event or censoring – date of first response + 1).

The time of the initial response will be defined as the latest of the dates contributing towards the first visit response of PR or CR (which was subsequently confirmed). The end of response should coincide with the date of PD or death from any cause used for the PFS endpoint based on RECIST 1.1. If a patient does not have PD following a response, then their duration of response will use the PFS censoring time.

6.4.3.5 Progression-Free Survival

Progression-free survival (PFS) is defined as the time from first dose of any study drug until the date of objective disease progression according to RECIST 1.1 or death (by any cause in the absence of progression) regardless of whether the patient withdraws from study therapy or receives another anti-cancer therapy prior to progression (i.e. date of PFS event or censoring – date of first dose + 1).

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 after two or more missed visits, the patient will be censored at the time of the latest evaluable RECIST assessment prior to the two missed visits. For all modules, the schedule of assessments is 6 weekly following the first dose of combination therapy, until 24 weeks. With the exception of Module 6 the schedule of assessments changes to 8 weekly after 24 weeks; for Module 6 the schedule changes to 9 weekly after 24 weeks. See below for details on calculating 2 missed visits between the last evaluable RECIST assessment (before the event) and the event.

Table 5: Calculating 2 missed visits between last evaluable RECIST assessment for all modules except Modules 2, 3, 6 and 10

Last evaluable RECIST assessment before event	Length of time of 2 missed visits
Baseline	2 x 6 weeks + 1 week for late assessment = 13 weeks
RECIST visit 1	2 x (6 weeks + 1 week) = 14 weeks
RECIST visit 2	2 x (6 weeks + 1 week) = 14 weeks
RECIST visit 3	6 weeks + 1 week + 8 weeks + 1 week = 16 weeks
RECIST visit 4	2 x (8 weeks + 1 week) = 18 weeks
RECIST visit 5 etc.	2 x (8 weeks + 1 week) = 18 weeks

For Modules 2, 3 and 10, there is a lead-in period of 7 days, i.e. one week. This will increase the baseline length by one week. Hence the below table will be used for calculating the 2 missed visits between the last evaluable RECIST assessment (before the event) and the event for Modules 2, 3 and 10:

Table 6: Calculating 2 missed visits between last evaluable RECIST assessment for Modules 2, 3 and 10

Last evaluable RECIST assessment before event	Length of time of 2 missed visits
Baseline	2 x 6 weeks + 1 week for late assessment + 1 week of lead-in + 2 days for late assessment for Cycle 1 Day 1 = 14 weeks + 2 days = 100 days
RECIST visit 1	2 x (6 weeks + 1 week) = 14 weeks
RECIST visit 2	2 x (6 weeks + 1 week) = 14 weeks
RECIST visit 3	6 weeks + 1 week + 8 weeks + 1 week = 16 weeks
RECIST visit 4	2 x (8 weeks + 1 week) = 18 weeks
RECIST visit 5 etc.	2 x (8 weeks + 1 week) = 18 weeks

For Module 6, the RECIST assessment is every 6 weeks ± 1 week for the first 24 weeks relative to the date of first dose (Cycle 1 Day 1), then every 9 weeks ± 1 week thereafter, until objective disease progression as defined by RECIST 1.1 and confirmed with a subsequent scan (in the absence of clinically significant deterioration).

Table 7: Calculating 2 missed visits between last evaluable RECIST assessment for Module 6

Last evaluable RECIST assessment before event	Length of time of 2 missed visits
Baseline	2 x 6 weeks + 1 week for late assessment = 13 weeks

RECIST visit 1	2 x (6 weeks + 1 week) = 14 weeks
RECIST visit 2	2 x (6 weeks + 1 week) = 14 weeks
RECIST visit 3	6 weeks + 1 week + 9 weeks + 1 week = 17 weeks
RECIST visit 4	2 x (9 weeks + 1 week) = 20 weeks
RECIST visit 5 etc.	2 x (9 weeks + 1 week) = 20 weeks

If the patient has no evaluable visits or does not have baseline data, they will be censored at Day 1 (first dose of any study drug) unless they die within 2 visits of baseline (For all modules except Modules 2, 3 and 10: 13 weeks, i.e. 12 weeks plus 1 week allowing for a late assessment within the visit window. For Modules 2, 3 and 10: 100 days i.e. 12 weeks plus 1 week allowing for a late assessment within the visit window + 1 week of lead in cycle + 2 days of Cycle 1 Day 1 window).

The PFS time will always be derived based on scan dates, not visit dates. Missing or partially incomplete scan dates will not be imputed.

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

- Date of PD (unconfirmed or subsequently confirmed) will be determined based on the **earliest** of the assessment/scan dates that led to assignment of an overall visit response PD by RECIST 1.1
- When censoring a patient for PFS the patient will be censored at the **latest** of the RECIST 1.1 assessment/scan dates contributing to a particular overall visit assessment

Overall visit assessments will be determined programmatically for each assessment (scheduled or unscheduled) and will contribute to the derivation of PFS.

Note: for TLs only the latest scan date is recorded out of all scans performed at that assessment for the TLs and similarly for NTLs only the latest scan date is recorded out of all scans performed at that assessment for the NTLs.

6.4.3.6 CCI [redacted]

CCI [redacted]

6.4.3.7 CCI [redacted]

CCI [redacted]

CCI

[redacted]

6.5 Safety Assessments

6.5.1 Duration of Exposure

Duration of exposure of patients will be assessed for each study drug. The planned treatment schedule of each study drug in each of the treatment modules is described in Section 6 of module-specific protocol appendices.

Duration of exposure will be evaluated in number of days (rescaled to months) for each of the study drugs as described in the table below:

Table 8: Total and Actual Treatment Durations

Study Drug	Total Treatment Duration (days)*	Actual Treatment Duration (days)*
Durvalumab (IV) [Modules 1, 2, 3, 4, 5, 7, 9, 10]	(min (last infusion date + 27, date of death, cut-off date)– first infusion date + 1).	Total treatment duration – any dose delays
Durvalumab (IV) [Module 6]	(min (last infusion date + 20, date of death, cut-off date)– first infusion date + 1).	Total treatment duration – any dose delays
Olaparib (tablet) [Module 1]	(Last dose date – first dose date + 1).	Total duration – any dose interruptions and planned non-dosing days **

Sponsor:	AstraZeneca	Protocol/CIP Number:	D6185C00001/Multiple drugs
CIL Project Number:	40773		

Study Drug	Total Treatment Duration (days)*	Actual Treatment Duration (days)*
AZD9150 (IV) [Module 2]	• (Last infusion date – first infusion date + 1), if the last cycle is Cycle 0 and there were less than 3 doses. • (min (last infusion date + 6, death date, cut-off date) - first infusion date + 1), for all other cases.	Total treatment duration – any dose delays.
AZD6738 (tablet) [Modules 3, 8, 9, 10 and 11]	(Last dose date – first dose date + 1).	Total treatment duration – any dose interruptions and planned non-dosing days **
Vistusertib (tablet) [Module 4]	(Last dose date – first dose date + 1).	Total treatment duration – any dose interruptions and planned non-dosing days **
Olecumab (IV) [Module 5]	• (min (last infusion date + 13, death date, cut-off date) – first infusion date + 1), if the last cycle is Cycle 1 or 2. • (min (last infusion date + 27, death date, cut-off date) – first infusion date + 1), for all other cases.	Total treatment duration – any dose delays.
Trastuzumab Deruxtecan (DS-8201a) (IV) [Module 6]	(min (last infusion date + 20, date of death, cut-off date) – first infusion date + 1).	Total treatment duration – any dose delays
Cediranib (AZD2171) (tablet) [Module 7]	(Last dose date – first dose date + 1).	Total treatment duration – any dose interruptions and planned non-dosing days

*The total and actual treatment duration is then rescaled to months using the below formula:

Sponsor:	AstraZeneca	Protocol/CIP Number:	D6185C00001/Multiple drugs
CIL Project Number:	40773		

Total or actual treatment duration (months) = Total or actual treatment duration (days) / (365.25/12)

**: For the calculation of actual treatment duration, if patient received one dose on any day (even Day 1), this will contribute to '0.5' day for the actual treatment duration. If the patient received two doses, this will contribute to '1' day for the actual treatment duration.

The calculation of treatment durations and relative dose intensity will not be performed where the study drug administration details are missing in the exposure although the drug accountability logs indicate that the patient received the study drug.
Exposure will also be measured by the number of cycles started (for drugs which are administered in cycles). A cycle corresponds to a period of 28/21 days as applicable. A cycle will be counted if treatment is started even if the full dose is not delivered. If a cycle is prolonged due to toxicity, this should still be counted as one cycle.

Dose modifications

The Study Treatment Log records dosing details for each dosing day.

Dose interruption is recorded in the treatment log and excludes any planned interruptions in accordance with the CSP. For the IV drugs, drug interruptions will be recorded if there is an interruption/break during the infusion, i.e. infusion interruptions during infusion. For the non-IV drugs, drug interruptions will be recorded if the study drug is temporarily stopped for some time interval.

Dose delays will be recorded for IV drugs only. If there is a delay in start of the IV infusion, then this will be recorded as dose delay.

Dose reductions are recorded in the treatment log. Dose modification is defined as the total number of reductions, interruptions or dose delays (IV drugs) recorded in the treatment logs.

For the non-IV study drugs, missed and forgotten doses should be recorded on the corresponding CRF module (EXL, EXL1, EXL2, …) as a dose interruption with the reason recorded appropriately. These missed or forgotten doses will not be included as dose interruptions in the summary tables, but the information will appear in the listing for dosing. However, these missed and forgotten doses will be excluded in the derivation of actual exposure.

Further details on dose modification of the individual study drugs are detailed in respective modules of the CSP.

Time to first dose delay (only for IV drugs) and dose interruptions (for all study drugs) will be evaluated.

Time to first delay/interruption will be calculated as:

Date of first dose delay/interruption – Date of first dose of study drug +1.

Dose Intensity

Dose Intensity for each of the study drugs will be addressed by considering relative dose intensity (RDI).

Relative dose intensity (RDI) is the percentage of the actual dose amount delivered relative to the intended dose amount through to treatment discontinuation.

$$\text{RDI} = \frac{d}{D} \times 100\%$$

where d is the actual cumulative dose in mg delivered up to the actual last day of dosing where last day of dosing is min(date of last dose date where dose > 0, date of death, date of DCO). D is the intended cumulative dose in mg up to the actual last day of dosing. D is the total dose that would be delivered if there were no modification to dose or schedule.

When deriving actual dose administered for infusion administered medications, the volume before and after infusion will also be considered.

6.5.2 Adverse Events

An AE is defined as the development of any untoward medical occurrence in a patient or clinical study patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence.

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

A TEAE is defined as follows:

- For patients not re-allocated to a second HUDSON treatment cohort: A TEAE is defined as an event with an onset date or worsening in CTCAE grade on or after the date of first dose of any study drug and up to and including 90 days following the date of last dose of study drug.
- For patients re-allocated to a second HUDSON treatment cohort: A TEAE is defined as any AE that started or worsened in CTCAE grade on or after the first dose of any study drug from the first cohort, until 90 days follow-up after discontinuation of study drug from the first cohort, unless the investigator assessed the

relatedness of the AE with onset during this interval to the non-durvalumab study drug from the second cohort.

- For patients in Module 11 who went on to receive durvalumab + ceralasertib combination therapy as subsequent therapy:
  A TEAE is defined as any AE that started or worsened in CTCAE grade on or after the first dose of ceralasertib monotherapy, until 90 days follow-up after discontinuation of ceralasertib monotherapy unless the investigator assesses the AE with onset during this interval to be related to ceralasertib or durvalumab and the AE started after initiation of durvalumab.

For the re-allocated patients, only AEs occurring in the first cohort will be considered for summaries. AEs occurring in the second cohort will be flagged in the datasets and presented in listings only.

Classification of the AE as a Cohort 1 AE or a Cohort 2 AE will be determined by whether the drug recorded in the "Other Study Drug" field of the AE page was taken during Cohort 1 or Cohort 2.

Any AE occurring within the defined 90-day follow-up period after discontinuation of study drug, with the exception of those with onset during this interval for which the investigator assessed the relatedness to the non-durvalumab study drug from the second cohort, will be included in the AE summaries. AEs occurring after the 90-day follow-up period after discontinuation of study drug, and AEs with onset during the defined 90-day follow-up period after discontinuation of study drug from the first cohort for which the investigator assessed the relatedness of the AE to the non-durvalumab study drug from the second cohort, will be listed separately, but not included in the summaries.

For patients from module 11 who switched to durvalumab combination, any AE occurring within the defined 90-day follow-up period after discontinuation of ceralasertib monotherapy, except for those with onset during this interval after initiation of durvalumab for which the investigator assesses the AE to be related to ceralasertib or the durvalumab, will be included in the AE summaries. AEs occurring after the 90-day follow-up period after discontinuation of study drug, and AEs with onset during the defined 90-day follow-up period after discontinuation from ceralasertib monotherapy for which the investigator assesses the AE to be related to ceralasertib or durvalumab and the AE started after initiation of durvalumab, will be listed separately, but not included in the summaries.

Any AE occurring before the first dose of study drug (i.e., before Cycle 0, Day 1, or Cycle 1, Day 1, as appropriate for each study cohort) will be included in the data listings but will not be included in the summary tables of AEs. In general, summary tables will include only TEAEs.

For Screen Failure patients (patients who signed the pre-screening ICF to participate in the study but did not meet the criteria for participation in the study, or were not subsequently assigned to a treatment cohort, or were assigned to a treatment cohort but not dosed), only SAEs and procedure related AEs will be collected.

Drug-related TEAEs will be defined as any TEAE with a causal relationship to study treatment for any study drug as assessed by the investigator.

6.5.2.1 AEs of Special Interest, AEs of Possible Interest and immune-mediated AEs

AEs of special interest for non-durvalumab drugs

Selected individual preferred terms and higher-level terms have been considered to be "AESIs" for each applicable non-durvalumab study drug in HUDSON. AESIs represent pre-specified risks that are considered to be of importance to a clinical development program. These AESIs have been identified as a list of preferred terms provided by the patient safety team for each of the specific drugs.

Other categories may be added as necessary or existing terms may be merged. An AstraZeneca medically qualified expert after consultation with the Global Patient Safety Physician has reviewed the AEs of interest and identified which higher-level terms and which preferred terms contribute to each AESI. Further reviews may take place prior to DBL to ensure any further terms not already included are captured within the categories.

AEs of special interest and AEs of possible interest for durvalumab

Some clinical concepts (including some selected individual preferred terms and higher-level terms) have been considered "AEs of special interest" (AESI) and "AEs of possible interest" (AEPI) to the durvalumab program. All AESIs are being closely monitored in clinical studies using durvalumab alone, and durvalumab in combination with other anti-cancer agents.

AESIs are defined as AEs with a likely inflammatory or immune-mediated pathophysiological basis resulting from the mechanism of action of durvalumab and requiring more frequent monitoring and/or interventions such as corticosteroids, immunosuppressants, and/or endocrine therapy. Endocrine therapies include standard endocrine supplementation, as well as treatment of symptoms

resulting from endocrine disorders (for example, therapies for hyperthyroidism include beta blockers [e.g., propranolol], calcium channel blockers [e.g., verapamil, diltiazem], methimazole, propylthiouracil, and sodium perchlorate). In addition, infusion-related reactions and hypersensitivity/anaphylactic reactions are also considered AESIs.

AEPIs are defined as AEs that could have a potential inflammatory or immune-mediated pathophysiological basis resulting from the mechanism of action of durvalumab but are more likely to have occurred due to other pathophysiological mechanisms, thus, the likelihood of the event being inflammatory or immune-mediated in nature is not high and/or is most often or usually explained by the other causes. These AEs not routinely arising from an inflammatory or immune-mediated mechanism of action – typically quite general clinical terms that usually present from a multitude of other causes –are classified as AEPIs.

These AESIs and AEPIs have been identified as Pneumonitis, Hepatic events, Diarrhea/Colitis, Intestinal perforations, Adrenal Insufficiency, Type 1 diabetes mellitus, Hyperthyroid events, Hypophysitis, Hypothyroid events, Thyroiditis, Renal events, Dermatitis/Rash, Pancreatic events, Myocarditis, Myasthenia gravis, Guillain-Barre syndrome, Myositis, Infusion/hypersensitivity reactions and Other rare/miscellaneous. Other categories may be added or existing terms may be merged as necessary. An AstraZeneca medically qualified expert after consultation with the Global Patient Safety Physician has reviewed the AEs of interest and identified which MedDRA preferred terms contribute to each AESI/AEPI. A further review will take place prior to Database lock (DBL) to ensure any further terms not already included are captured within the categories.

Immune-mediated Adverse Events (imAE) for durvalumab

Durvalumab belongs to a class of drugs called immune checkpoint inhibitors. Because the mechanism of action of this class of drugs is to block the inhibitory signals that prevent T-cell activation, this drug may potentially cause immune-mediated adverse drug reactions (imAEs). imAEs will be identified from both AESIs and AEPIs based on programmatic rules that consider interventions involving systemic steroid therapy, immunosuppressant use, and/or endocrine therapy which, in the case of AEPIs, occurs after first considering an Investigator's causality assessment and/or an Investigator's designation of an event as immune-mediated. Endocrine therapies include standard endocrine supplementation, as well as treatment of symptoms resulting from endocrine disorders (for example, therapies for hyperthyroidism include beta blockers [e.g., propranolol], calcium channel blockers [e.g., verapamil, diltiazem], methimazole, propylthiouracil, and sodium perchlorate).

In addition, the Sponsor may perform medical review of those AESIs and classify them as imAEs or not imAEs via an independent manual adjudication process if required.

6.5.2.2 Procedure related AEs and SAEs

Procedure related AEs and SAEs only will be captured from the time of signature of the pre-screen informed consent for those patients who provide a new tumour biopsy during the study. AEs and SAEs occurring up to and including 21 days after the new tumour biopsy procedure completed during the study will be recorded and will be listed.

6.5.2.3 COVID-19 infection events

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

6.5.3 Clinical Laboratory Evaluations

Haematology, clinical chemistry, urinalysis (see Table 9 for the list of laboratory safety variables), and coagulation will be performed according to the times in the core and module-specific SoA in the protocol.

For Module 6, troponin-T (preferably high-sensitivity troponin-T) will be assessed at the timepoints as described in SoA along with standard laboratory assessments. If it is not possible to assess troponin T, then sites should assess troponin I instead. All samples for a patient should be assessed using the same Troponin test at the same laboratory throughout the study where feasible.

For Module 7, urine samples will be collected at Screening, on Cycle 1 Day 1, Cycle 1 Day 15, and Day 1 of each subsequent cycle and drug discontinuation to monitor for proteinuria. In addition, urinary protein/creatinine (UPC) ratio will be collected.

For Modules 3, 10 and 11 only, eosinophil and monocyte counts will be recorded as part of the routine white blood cell count safety assessment. For Module 3 patients already enrolled at the time of protocol version 10.0 in the expanded cohorts and who signed CSP v10.0 or onwards, counts could be recorded retrospectively.

All patients who have any CTCAE Grade 3 or 4 laboratory values at the time of completion or discontinuation from study treatment must have further tests performed until the laboratory values have returned to CTCAE Grade 1 or 2, unless these values are not likely to improve because of the underlying disease. The results of further tests will be presented as unscheduled visits. The results of unscheduled tests will be considered when summarising the data.

The clinical chemistry, haematology (including coagulation) and urinalysis will be performed at a local laboratory at or near the investigator site. All parameters will be converted to international system of units (SI) when presented in summary tables and listings.

Table 9: List of laboratory parameters

Sponsor:	AstraZeneca	Protocol/CIP Number:	D6185C00001/Multiple drugs
CIL Project Number:	40773		

Haematology/Haemostasis (whole blood)	**Urinalysis (dipstick)**
B-Haemoglobin	U-Blood
B-Platelet count	U-Colour and appearance
B-White blood cell (WBC) count	U-Ketones
B-Absolute neutrophil count (ANC)	U-pH
B-Absolute lymphocyte count (ALC)	U-Protein
B-Eosinophil count	U-Specific gravity
B-Monocyte count	
B-Red blood cell (RBC) count	
Clinical Chemistry (serum or plasma S/P)	
S/P-Albumin	S/P-Alkaline phosphatase (ALP)
S/P-Alanine aminotransferase (ALT)	S/P-Amylase
S/P-Aspartate aminotransferase (AST)	S/P-Total calcium
S/P-Chloride	S/P-Creatinine clearance
S/P-Creatinine	S/P-Gamma glutamyltransferase (GGT)
S/P-Direct bilirubin	S/P-Indirect bilirubin
S/P-Glucose (random)	S/P-Lactate dehydrogenase
S/P Lipase	S/P-Magnesium
S/P-Phosphate	S/P-Potassium
S/P-Sodium	S/P-Total bilirubin
S/P-Total protein	S/P-TSH

S/P-T_3 free (reflex)	S/P-T_4 free (reflex)
S/P-Urea or BUN, depending on local practice	S/P-CRP
S/P-Haptoglobin	S/P Troponin (Module 6 only)
Coagulation	
Activated partial thromboplastin time (APTT)	International normalised ratio (INR)
B/P-Fibrinogen	

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

Haematology, clinical chemistry, and coagulation values will be classified as low (L), normal, and high (H) according to the normal ranges. In addition, CTCAE grading (NCI CTCAE v4.03) taking values Grade 1, 2, 3, or 4, will be used to classify selected parameters.

Table 10: Laboratory Parameters with CTCAE grading

Haematology/Haemostasis (whole blood)	
Lymphocytes, particle concentration	Absolute neutrophil count
Platelets, particle concentration	Absolute lymphocyte count
Haemoglobin	
Clinical Chemistry	
Albumin	Alkaline phosphatase
Alanine aminotransferase	Amylase
Aspartate aminotransferase	Creatinine
Gamma glutamyltransferase (GGT)	Lipase
Phosphate	Total bilirubin
Clinical Chemistry Bi-directional CTCAE	
Magnesium	Total calcium
Potassium	Glucose (random)
Sodium	
Coagulation	
Activated partial thromboplastin time (APTT)	International normalised ratio (INR)

6.5.4 Other Observations Related to Safety

6.5.4.1 Vital Signs

Vital signs including blood pressure, pulse rate, body temperature, and respiration rate will be evaluated according to the SoA of the corresponding module of the study. Body weight is also recorded at each visit along with vital signs.

For Module 2, the blood pressure and pulse rate will be collected on Cycle 1 Day 1 (first infusion of durvalumab) prior to durvalumab infusion, during infusion, at end of infusion, and 1 hour after end of durvalumab infusion. It will be also collected at pre-dose for each cycle Day 1 and at C1D15 and C2D15.

For other modules, vital signs will be collected as per protocol.

6.5.4.1.1 Oxygen Saturation (Module 6)

SpO_2 will be measured to enhance the investigation and diagnosis of possible pneumonitis for all modules.
For Module 6, SpO_2 will be performed before and after infusion on Cycle 1 Day 1, Cycle 2 Day 1 and Cycle 3 Day 1, measured at any time at Cycle 1 Day 8 and Cycle 1 Day 15, and before infusion on Day 1 of each subsequent cycle (Cycle 4 Day 1 onwards), and at the end of treatment visit and the follow-up visit.

6.5.4.1.2 Additional Vital Signs measurements recorded by patients (Module 7 only)

All patients in Module 7 should check only their BP and pulse rate twice daily for at least the first 8 weeks after starting study drugs, or, if antihypertensive management is required, until a stable anti-hypertensive regimen has been established, overall for at least 8 weeks and even if this requires more than 8 weeks. Thereafter the monitoring can be reduced to once daily, but twice daily monitoring could be re-implemented (after any cediranib dose interruption for at least 2 weeks or until the patient is re-established on a stable antihypertensive regimen, whichever takes longer). Patients should continue to check their BP and pulse rate for as long as they remain on cediranib treatment and for 30 days after cediranib discontinuation.

Patients will record their BP and pulse data using handheld electronic devices, to be provided by the study Sponsor. In case there are any technical issues with the device, then the data will be collected in clinical database until the technical issue with the device is rectified. Thus the data will either come from external vendor or from specific pages of the CRF (VSL3) which will be used to

collect the home assessment data that could not be transferred electronically to external vendor. Any records with TASKSTAT = "Inactive" or "New" that have missing subject information from the vendor file will be disregarded and excluded from analysis.

For each patient, the average of all the available BP measurements for morning and evening will be calculated separately.

Morning and Evening Time periods:

Morning time period will be defined as the time between 0:00 hours and 11:59 hours. All the measurements (AM measurements) collected during this time frame will be used to calculate the morning average (AM average).

Evening time period will be defined as the time between 12:00 hours to 23:59 hours. All the measurements (PM measurements) collected during this time frame will be used to calculate the evening average (PM average).

Daily morning and evening average:

If a patient records more than one measurement in the morning of a day, then the average of these morning measurements will be calculated and considered for that daily morning average. If only one measurement is recorded in the morning of a day, then that record will be considered for that daily morning average.

A similar approach will be used to calculate the daily evening average.

6.5.4.2 Electrocardiograms

Triplicate 12-lead ECG will be assessed at screening and the timepoints specified in SoA.

For ECGs with normal overall evaluation, with borderline overall evaluation or with abnormal non-clinically significant finding the mean of the triplicate values of each ECG parameter will be recorded.

For ECGs with abnormal clinically significant finding, the ECG will be recorded in triplicate. The mean of the ECG parameters to be collected as triplicate will be calculated.

Continuous ECG parameters include heart rate, PR, RR, QRS and QT intervals. The QT intervals will be corrected for heart rate and calculated using

Fridericia correction: QTcF in msec = (QT in msec)/(RR in sec)$^{1/3}$

Categorical overall ECG interpretation (normal, borderline, abnormal) and whether clinically significant will also be provided.

6.5.4.3 Physical Examination

A complete physical examination (PE) will be performed at screening and data collected. Targeted physical examinations will be performed throughout the treatment period at the time specified in the module-specific SoA. The baseline abnormality of PE will report as medical history, 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.

Height will be measured at screening only.

6.5.4.4 ECOG (Eastern Cooperative Oncology Group) Performance status

The patient's performance status will be assessed at screening only using the ECOG/WHO Performance Status scale, please refer to Table 11.

Table 11: Eastern Cooperative Oncology Group Performance Status

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

6.5.4.5 Pregnancy Tests

Pregnancy tests will be performed for pre-menopausal women of childbearing potential as specified in the SoA.

6.5.4.6 Ophthalmologic assessments

For Module 6, ophthalmologic assessments will be performed as per the SoA of Module 6 CSP. The assessments will include:

- Visual acuity
- Slit lamp examination
- Fundoscopy.

Visual Acuity

Visual acuity is measured using two of the following three charters:

- Early Treatment Diabetic Retinopathy Study (ETDRS) -
  The ETDRS scores for both left and right eye will be collected in CRF
- Snellen Equivalent (Eqv) -
  The visual acuity scores will be collected either in 20/xx foot or 6/xx metre format for both left and right eye. The equivalent Snellen's score converted to decimals for both eyes will also be collected in CRF.
- Landolt Eqv -
  The visual acuity scores will be collected either in 20/xx foot or 6/xx metre format for both left and right eye. The equivalent Landolt's score converted to decimals for both eyes will also be collected in CRF.

The ETDRS is collected for all the patients. Only one of the pair of assessments among Snellen's or Landolt's equivalent will be collected throughout the study for a patient.

Slit lamp Examination

The slit lamp examination results (normal; abnormal, not clinically significant; abnormal, clinically significant) will be collected.

Fundoscopy

The fundoscopy results (normal; abnormal, not clinically significant; abnormal, clinically significant) will be collected.

6.5.4.7 LVEF

For Modules 6 and 7, LVEF will be measured using either echocardiogram (ECHO) or multi-gated acquisition (MUGA) scan and will be performed as per the SoA of respective modules.

6.6 Exploratory Variables

6.6.1 Overall Survival of Screen Failures

To investigate outcomes in patients who screen fail, the OS will be presented to support the interpretation of outcomes for treatment interventions. OS of screen failure patients is defined as the time in days from the date of pre-screen informed consent until death due to any cause + 1. 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 (Section 6.4.3.1). Survival status is being obtained for all screen fail patients who were screened before implementation of protocol version 10.0, until implementation of protocol version 10.0. As of protocol version 10.0, there is sufficient survival follow-up data for these patients.

The CRFs to be considered are as follows:

- Pre-screening informed consent date
- Main screening informed consent date
- Laboratory test dates
- Date of vital signs
- Date last known alive on survival status CRF
- Adverse event start and stop dates
- Date of consent withdrawal
- Start and stop dates of subsequent anti-cancer treatment

The aim will be to select a group of screen failure patients that can serve as a control group in an exploratory manner, to provide a context when interpreting the survival endpoints in the HUDSON dosed patients. The outcome of this analysis will not form a part of CSR but may be included in other documentation.

Propensity Scores (Rosenbaum and Rubin, 1983) will be used to create the control group. The propensity score is a patient's probability of treatment assignment, conditional on observed baseline covariates. The propensity scores will be estimated using a logistic regression model. Potential covariates in the model include baseline demographics, patient prognostic outcome scores, such as the Royal Marsden Hospital (RMH) score, the Gustave Roussy Immune (GRIm) score, prior history performance on immuno-oncology (IO) therapy, selected biomarkers within the HUDSON matched cohorts (Breast cancer associated gene (BRCA), Homologous recombination repair gene (HRR) mutation and Liver kinase B1 (LKB1)) and prior anticancer therapy.

Of note, where covariates are involved in determining an inclusion or exclusion (IE) criteria for HUDSON, a patient that fails screening on those particular IE criteria is unlikely to overlap fully with the HUDSON population by intent. They may overlap with a HUDSON cohort if they were not part of the specific IE criteria for that cohort.

All screen failure patients will be weighted by the ratio of the estimated propensity score to 1 minus the estimated propensity score, i.e. the odds of treatment assignment (Austin and Stuart, 2015). This will create a pseudo population that is similar in characteristics to the cohort dosed patients. Screen failure patients with extremely low weights would contribute negligible information to the final survival analysis and will not be included in the control group.

If there is insufficient overlap in any covariate distributions across the treated and control populations, the weighting will be performed without these covariates. The effective sample size of the screen failure patients after weighting will be calculated. If weighting based on the remaining covariates is not successful due to a very low effective sample size (<20 patients), then it may be considered necessary to include fewer covariates in the logistic regression.

To assess the performance of the weighting, histograms and summaries of the unweighted and weighted covariate distributions will be produced.

6.6.2 Pharmacokinetics

For Module 2 (durvalumab plus AZD9150), plasma or serum concentrations for AZD9150 will be measured.

For Module 6 (durvalumab plus trastuzumab deruxtecan), plasma or serum concentrations for durvalumab and trastuzumab deruxtecan will be measured. In addition, for the patients who receive chloroquine or hydroxychloroquine treatment, additional trastuzumab deruxtecan PK samples will be taken at the following timepoints during the chloroquine/hydroxychloroquine treatment period:

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

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

For Module 7 (durvalumab plus cediranib), plasma or serum concentrations for cediranib will be measured.

For Module 10 (durvalumab plus AZD6738), plasma or serum concentrations for durvalumab and AZD6738 will be measured.

6.6.3 Immunogenicity

Presence of ADA for durvalumab will be assessed in samples from those patients receiving durvalumab treatment in any study module according to the SoA (all modules except Modules 8 and 11). In addition, presence of ADA for trastuzumab deruxtecan will be assessed in samples from those patients receiving trastuzumab deruxtecan treatment in Module 6. In addition, ADA samples will be analysed for AZD9150 in Module 2.

The collection of ADA samples for oleclumab in Module 5 was removed from CSP version 6. Positive samples for the presence of ADAs will have to be confirmed, and for those samples confirmed positive for the presence of ADAs immunogenicity, titer will be reported.

6.6.4 Other Exploratory Variables

The other exploratory variables include plasma [redacted] MAF, the immune-related markers, genetic aberrations, post-baseline biopsies and DNA derived from blood samples will not form part the CSR and hence are not included in this SAP.

The molecular profile of biopsies and [redacted] collected at pre-screening will be reported in the CSR as these determine allocation to cohorts and overall eligibility.

7 STATISTICAL METHODS

7.1 General Methodology

For categorical data, the number and percentage of patients in each category will be presented. Percentages by categories will add up to 100%, i.e. percentage denominators will be based on the number of patients with no missing data, or the categories summarised will include a missing category. Percentages will be displayed to 1 decimal place. No percentage will be displayed for zero counts, and no decimal will be presented when the percentage is 100%.

For continuous data, descriptive statistics will include number of patients with non-missing measurements (n), mean, standard deviation (SD), median, minimum and maximum. When needed, the use of other percentiles (e.g. 25% (first quartile Q1) and 75% (third quartile Q3)) will be mentioned in the relevant section. If n is less than 3, the mean, SD, median, Q1 and Q3 will not be reported.

Decimal places for descriptive statistics will always apply the following rules:

- n will be presented as integers.
- Mean, median, Q1 and Q3 will be presented as the original value +1 additional decimal place.
- SD and geometric mean will be presented as the original value +2 additional decimal places, but up to a maximum of 3 decimal places.
- Minimum and maximum will have the same number of decimal places as the original value.
- In case the original value is reported for 4 or more decimals, then number of decimal places presented in the displays will be limited to 4 decimal places for every statistic.

Summaries for the patient disposition, demographics, baseline characteristics, medical history, prior and concomitant medications, efficacy and safety variables will present results by cohort (biomarker-matched type or immunotherapy resistance type (primary or acquired resistance) to prior PD-1/PD-L1 therapy or dose group) and total, within each treatment module as appropriate.

Re-allocated patients will be summarised in their first cohort only, and no summaries are expected in their second cohort. Safety data following re-allocation to the second cohort will be included only in separate listings. The list of re-allocated patient listings is identified in the Section 11 of the SAP. The listings for re-allocated subjects will display baseline characteristics and demographics data as assessed prior to the first cohort. Prior anti-cancer therapy, prior radiotherapy, medical and surgical history, subsequent anti-cancer therapy and subsequent radiotherapy will be relative to the first cohort. Listings for re-allocated subjects will not be produced if there are no subjects in the analysis set planned to be used when generating that listing.

A different approach may be necessary in future while reporting individual modules as necessary. Accordingly, the SAP will be amended.

For patients from Module 11 who will go onto the combination therapy after disease progression, data on the combination therapy will be collected as any other subsequent anti-cancer therapy but not reported except for some specific TEAEs detailed in 6.5.2. If the data subsequently needs to be reported, the SAP will be updated accordingly.

Extent of laboratory, ECG and vital signs data to be included in summary tables, figures and listings:

Sponsor:	AstraZeneca	Protocol/CIP Number:	D6185C00001/Multiple drugs
CIL Project Number:	40773		

For the patients not re-allocated to a second HUDSON treatment cohort: The data from baseline up to 90 days after discontinuation of study drug will be included.

For patients re-allocated to a second HUDSON treatment cohort and patients in Module 11 who received durvalumab + ceralasertib combination therapy as subsequent therapy: The data from baseline up to the earliest of the following will be included.

- First dose of study drug in the second cohort, or for Module 11 first dose of study drug in durvalumab + ceralasertib combination therapy
- 90 days after discontinuation of study drug from the first cohort, or for Module 11 90 days after discontinuation from ceralasertib monotherapy

The study design allows modular CSR and hence displays will be produced to support modular CSR. All the data displays will be produced per module. Within each module the data will be displayed per cohort and per biomarker classification, or by dose group. The displays for each module will be labelled appropriately so that they are unique from each other. The data displays for the modular CSR will be produced following the data cut-off for the analysis of all the cohorts (or dose groups) in the respective module. Final analysis of each module will be performed after the planned database lock for the module which can occur either 12 months after the last patient has started treatment or when 75% of the patients have died.

The quarterly review (QR) outputs will provide tolerability and safety data and will also give a reasonable chance of detecting any efficacy signal in this cohort, should one exist.

Overall survival and progression-free survival across all cohorts for ITT patients will be presented at the end of the study.

For the modules that are terminated, for example Module 4, the full set of CSR data displays might not be required. Instead, data displays may include listings only (subset of CSR listings). This requirement will be discussed and agreed by the Sponsor. All the data displays will support the analysis required for CSR which is described in this SAP [redacted]

7.1.1 Potential impact of COVID-19

The following outputs will help assess the impact on the COVID-19 pandemic. A summary and listing of patients impacted by the pandemic, including details of whether the impact related to study visits, study drug administration, concomitant medication usage, study drug or study

discontinuation. The summary of patient disposition will include the number and percentage of patients who discontinued study drug and discontinued the study due to COVID-19. The summary of important protocol deviations will summarise all important protocol deviations, as well as COVID-19 related important protocol deviations (IPD) and non-COVID-19 related important protocol deviations. Patients with reported issues in the Clinical Trial Management Systems due to COVID-19 pandemic will be listed irrespective of whether the deviation is considered as important.

The outputs will be reviewed to identify whether patients missed 2 or more RECIST scans due to COVID-19, to assess whether the analysis of PFS data is impacted by the pandemic. The listing of SAEs will be reviewed for evidence of excess deaths due to COVID-19 (e.g., undiagnosed deaths due to COVID-19). Additional outputs as necessary will be produced.

7.2 Adjustments for Covariates

Not applicable for this study.

For OS for screen failures analyses, please refer to Section 6.6.1.

7.3 Handling of Dropouts or Missing Data

7.3.1 Imputation of Adverse Event Onset Date

Missing onset dates (where in eCRF UN, UNK and 0000 indicate unknown or missing Day, Month and Year respectively for partial missing dates; while completely missing dates would be left empty) will be imputed according to the following rules:

- Completely missing dates will not be imputed.
- If the day is missing and the month and year are different from the month and year of the first dose of any study drug, assume 01-MMM-YYYY. If the month and year are the same as the date for the pre-screen consent, then assume the pre-screen consent date for the onset date unless the month and year is also the same as the date of the first dose of any study drug and the following applies. If the month and year are the same as the first dose of any study drug, month and year and the end date (after any imputation) is on or after (including still on-going at the end of the study) the first dose of any study drug, then assume the date of the first dose of any study drug. If the month and year are the same as the first dose of any study drug, month and year and the end date (after any imputation) is prior to the first dose of any study drug, then assume the end date for the onset date.
- If the month is missing and the year is different from the year of first dose of any study drug, assume 01-JAN-YYYY of the collected year. If the year is the same as the date for the pre-screen consent, then assume the pre-screen consent date for the onset date unless

the year is also the same as the date of the first dose of any study drug and the following applies. If the year is the same as the first dose of any study drug year and the end date (after any imputation) is on or after (including still on-going at the end of the study) the first dose of any study drug, then assume the date of the first dose of study drug. If the year is the same as the first dose of any study drug and the end date (after any imputation) is prior to the first dose of any study drug, then assume the end date for the onset date.

After applying these rules, if the imputed AE onset date is after a complete AE end date (or date of death), the imputed onset date will be the same as the complete AE end date (or date of death).

Of note is that missing start dates for concomitant medications will not be imputed.

7.3.2 Imputation of Adverse Event / Concomitant Medication Stop Date

Missing stop dates will be imputed according to the following rules:

- Completely missing dates will be not imputed
- If the day is missing: Assume the last day of the month
- If the month is missing: Assume 31-DEC-YYYY.

After applying these rules:

- If the imputed AE or concomitant medication (CM) stop date is after the date of death, the imputed stop date will be the same as the date of death.
- If the imputed AE or CM stop date is after the DCO, then AE/CM will be ongoing and associated variables should be reset accordingly.

If the AE/CM is ongoing, the stop date will remain missing.

7.3.3 Imputation of Death Dates

Missing death dates will be imputed according to the following rules:

- If only the day is missing then the date will be imputed at the last day of the previous month recorded.
- If month is missing then the date will be imputed at the last day of the previous year recorded.

7.3.4 Imputation of EOT Dates

Missing EOT dates will be imputed according to the following rules:

- If only the day is missing then the date will be imputed at the maximum date between the last day of the previous month recorded and the last day of exposure.

- If month is missing then the date will be imputed at the maximum date between the last day of the previous year recorded and the last day of exposure.

7.3.5 Imputation of Subsequent Cancer Therapy Start Date

Missing subsequent cancer therapy start date will be imputed according to the following rules:

- Completely missing dates will be not imputed
- If only the day is missing then the date will be imputed at the later of:
  - 01-MMM-YYYY
  - 1 day after the last dose of study treatment
- If month is missing then the date will be imputed at the later of:
  - 01-JAN-YYYY
  - 1 day after the last dose of study treatment

7.3.6 Imputation of Diagnosis Date

Missing diagnosis date will be imputed according to the following rules:

- Completely missing dates and if day and month are missing will be not imputed.
- If only the day is missing then the date will be imputed at the 15th of the month.

7.3.7 Imputation of Laboratory values

Laboratory values of the form of "< x" (ie, below the lower limit of quantification) will be imputed as "0.99x LLOQ" in the calculation of summary statistics but displayed as "< x" in the listings. Laboratory values of the form ">x" (ie, above the upper limit of quantification) will be imputed as "1.01*ULOQ" and the value ">x" will be displayed in the listings. Note that 0 should not be used as an imputed value in case the endpoint requires a log transformation.

7.3.8 Interim Analyses and Data Monitoring

7.3.8.1 Data Monitoring

Every 3 months, analysis and reporting will be performed for key efficacy and safety variables. These Quarterly Review (QR) outputs will be reviewed by the HUDSON clinical program team (CPT) in case decisions about cohort expansion can be made. Also the safety outputs will be

provided for review by an external independent data monitoring committee (IDMC). The IDMC will be composed of therapeutic area experts and a biostatistician, who are not employed by AstraZeneca and are free from conflict of interest. Following the reviews, the IDMC will recommend whether the study should continue without any modifications, be amended, or whether study modules or the entire study should be terminated. Once the IDMC has reached a recommendation, a recommendation memo will be provided to AstraZeneca. If the IDMC recommends termination of a cohort or module for safety reasons, the IDMC Chairperson will send the recommendation memo and closed report to the Vice President Oncology Clinical Development, AZ. The final decision to modify or stop the study will sit with the sponsor. The timing of the above reviews may be modified, and/or additional safety reviews added, based on recommendation by the IDMC. Full details of the IDMC procedures and processes can be found in the IDMC Charter. The safety of all AstraZeneca/MedImmune clinical studies is closely monitored on an ongoing basis by AstraZeneca/MedImmune representatives in consultation with the Patient Safety Department. Issues identified will be addressed; this could involve, for instance, amendments to the CSP and letters to investigators.

7.3.8.2 Interim Analysis

This section describes fully the interim analysis (IA); there will be no separate interim analysis plan. The list of outputs included in the QR analysis report is maintained in dedicated shell TLFs documentation as the QR analysis report is not exactly a subset of the CSR outputs. A certain amount of modifications is implemented for the QR analysis to assist IA. Additional specific analysis details are maintained separately along with Section 11 of this document, which describe these changes to the quarterly report.

An IA of efficacy will be conducted in each cohort after approximately the CCI evaluable patient in that cohort, or the final patient dosed in a cohort if enrolment has ended early, has had the opportunity for two on-treatment RECIST assessments or has discontinued or withdrawn from treatment. This analysis may be flexibly timed to coincide with the QR of efficacy and safety outputs. Exceptions to this for individual treatment cohorts are described later in this section.

There will be approximately CCI evaluable patients in each treatment cohort, with 2 options for possible expansion should an efficacy signal, such as 4 or more observed confirmed responses (CR, PR), be observed. Alternatively, patients could be enrolled to a non-comparative randomized expansion where approximately an additional CCI patients could be randomized to either study treatment or standard of care/treatment of physician's choice (to be determined and defined in the resulting CSP amendment).

For Module 9, enrolment of approximately CCI evaluable patients was planned in each treatment cohort (ACQ and PRI). This was based on encouraging preliminary data from Module 3. Data were to be reviewed after the first CCI patients in each treatment cohort and continue up to CCI evaluable

patients unless the emerging data review indicated a less than expected efficacy signal. Enrolment continued during the review of the data. Following a regular data review (data cut-off 26 October 2021), the decision was made by AstraZeneca to close recruitment to Module 9 (both Cohorts B.9.ACQ and B.9.PRI) and to re-open/expand Module 3 (Cohorts B.3.ACQ and B.3.PRI). Per protocol version 10.0 for Module 3, cohorts B.3.ACQ and B.3.PRI and A.3.ATM were expanded and as per protocol version 12.0 all three cohorts have been closed for enrollment.

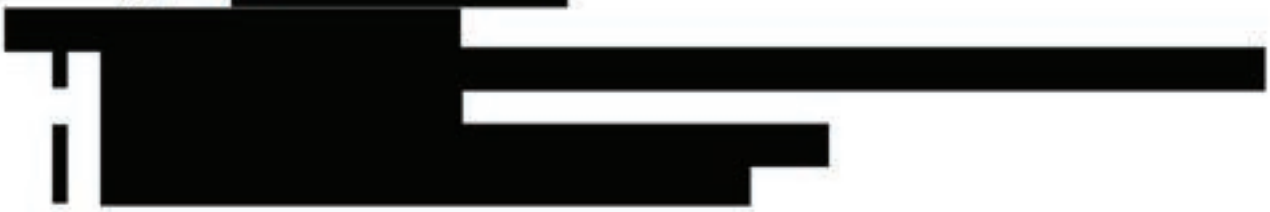
Per protocol version 10, Module 10 (in Group C) is included in this study. Introduction of Module 10 follows regulatory recommendation to gather additional data on the impact of different doses of AZD6738 to support a registration-based Phase 3 study; therefore, the study decision framework does not apply to this module. For Module 10, an interim analysis will be performed at least 24 weeks following approximately CCI patient in the 160 mg cohort and approximately CCI patient in the 240 mg cohort first dose, or when the approximately CCI patient in the 160 mg cohort or approximately CCI patient in the 240 mg cohort have discontinued or withdrawn from the treatment. Based on observed efficacy, safety and tolerability data, each cohort may be increased to up to C patients.

A recommendation to stop a module will be made utilizing the following safety No-Go decision criteria: STOP if the observed one-sided 90% lower confidence limit of the discontinuation rate, from either investigational product (IP), due to any adverse events is greater than or equal to 20%. For example, with 20 patients, this equates to observing a discontinuation rate due to adverse events greater than or equal to 7/20 (35%). The IDMC will be provided with No-Go criteria specific to the number of evaluable patients. There is only one planned No-Go assessment of discontinuation rate due to adverse events within each module when at least C evaluable patients in a module have had the opportunity for 12 weeks exposure. The decision criteria were developed using the methodology from Frewer et al (2016) with a Lower Reference Value (LRV)=35% and a Target Value (TV)=20%. Repeated use of these criteria within a module will require agreement from the Sponsor.

Per protocol version 11, Module 11 (in Group C) is included in this study. Introduction of Module 11 is to further investigate the contribution of components of AZD6738 as monotherapy, as it is considered to be active in the combination setting with durvalumab. Therefore the decision framework is a recommendation only and any decision to stop or expand at any time will be at the discretion of the sponsor and will be based on emerging efficacy, safety and tolerability data. For Module 11, a futility analysis will be carried out after approximately the CCI evaluable patient in the cohort has had the opportunity for 2 on-treatment RECIST assessments or has discontinued or withdrawn from treatment. If the futility criteria are not met (>0 confirmed responses (CR or PR) out of the C patients), the cohort will be expanded and a second interim analysis will be carried out after the CCI evaluable patient in the cohort, or the final patient dosed in the cohort if enrolment has ended early, has had the opportunity for 2 on-treatment RECIST assessments, or has

discontinued or withdrawn from treatment. There is the potential option to expand the cohort to [redacted] patients, should an efficacy signal, such as more than 4 confirmed responses out of the [redacted] patients, be observed, and supported by emerging data (including progressive disease rate, time to progression, discontinuation rate and death rate). The interim analysis will provide tolerability and safety data and will also give a reasonable chance of detecting any efficacy signal in this cohort, should one exist.

7.4 CCI [redacted]



The following summary/listings are planned CCI [redacted]

- Disposition (Listing only)
- Demography
- Disease characteristics
- Extent of disease (Listing only)
- Pathology of non-small cell lung cancer (Listing only)
- Previous disease-related treatment modalities (Summary only)
- Previous disease-related systemic anti-cancer treatment (Summary only)
- Prior anti-cancer treatment (Listing only)
- Prior radiotherapy (Listing only)
- Tumour biomarker profile
- Subsequent cancer therapy
- Adverse Events and SAE (from the time of signature of the pre-screen ICF throughout the safety follow-up). SAE will be listed only
- Overall Survival (with Kaplan-Meier plot)

Further details are provided in respective sections.

Sponsor:	AstraZeneca	Protocol/CIP Number:	D6185C00001/Multiple drugs
CIL Project Number:	40773		

8 STATISTICAL ANALYSIS

8.1 Disposition of Patients

Disposition and reasons for study discontinuation will be summarised for Enrolled Patients (which includes patients who sign the prescreening ICF and have their treatment module allocated at pre-screening) and will be displayed for total patients only. Disposition and reasons for discontinuation of each study drug will be summarised for Enrolled Patients with treatment allocation and the Intention-to-Treat (ITT) analysis set; and will be displayed by cohort (or dose group, as applicable) and module-specific total. The three reasons of discontinuation - objective progression confirmed progression and symptomatic deterioration will be presented under a category "Evidence of disease progression". Other reasons of discontinuation will be presented as per eCRF.

A list of patient disposition will be provided for Enrolled Patients and for Screen failures.

8.2 Protocol Deviations

Study specific important protocol deviations (IPD) will be defined in the Early Clinical Development Non-compliance Handling Plan (ECD NHP). The list of IPDs will be finalized prior to database lock.

Important protocol deviations may include, but are not limited to the following:

1. Those who entered the study even though they did not satisfy the entry criteria (ICH E3). Inclusion criteria
2. Those who entered the study even though they did not satisfy the entry criteria (ICH E3). Exclusion criteria
3. Those who developed discontinuation/ withdrawal criteria during the study but were not withdrawn from treatment (ICH E3).
4. Those who developed discontinuation/ withdrawal criteria during the study but were not withdrawn from Study (ICH E3).
5. Subject received the wrong treatment or incorrect dose. (ICH E3).
6. Subject received prohibited medications (ICH E3).
7. Deviations related to Study Procedure.
8. Other Important Protocol Deviations.

None of the deviations will lead to subjects being excluded from any analysis populations described in the SAP, unless otherwise specified. If a deviation is serious enough to have a potential impact on the primary analysis, sensitivity analyses may be performed. A list of all protocol deviations will

be reviewed and decisions regarding how to handle these deviations documented by the study team physician, clinical pharmacology scientist and statistician prior to database lock.

The incidence of important protocol deviations (IPDs) will be summarised for the ITT analysis set for deviation categories by cohort and module-specific total. The number and percentage of subjects in the following categories will be summarised:

- Number of subjects with at least 1 important protocol deviation
- Number of subjects with at least 1 COVID-19 related important protocol deviation
- Number of subjects with at least 1 important protocol deviation, excluding COVID-19 related IPDs

Patients with more than one IPD in a category will be counted only once in the summary of that IPD category. A list of patients with IPDs will be provided for the ITT analysis set.

8.3 Analysis sets

The analysis sets are summarised in Table 12. The number of patients included/excluded from each of the analysis sets (except Screen Failures analysis set) will be summarised by cohort and module-specific total for patients who were allocated to a treatment cohort within each module. Reasons for exclusion from analysis sets will be summarised for every population and listed for the ITT population.

Table 12: Study Analysis Populations

Population	Description
Enrolled Patients	Enrolled Patients is defined as all patients who sign the pre-screening ICF and had their treatment module allocated at pre-screening.
Screen Failures	Patients who signed the pre-screening ICF to participate in the study but did not meet the criteria for participation in the study, or were not subsequently assigned to a treatment cohort, or were assigned to a treatment cohort but not dosed.
Safety Analysis Set (SAF)*	All enrolled patients who took ≥ 1 dose of study drug. Patients will be analysed according to the actual treatment received and corresponding assigned cohort.
Intention To Treat (ITT)	All enrolled patients who took ≥ 1 dose of study drug. Patients will be analysed according to their assigned cohort and planned treatment.

Sponsor:	AstraZeneca	Protocol/CIP Number:	D6185C00001/Multiple drugs
CIL Project Number:	40773		

Population	Description
Evaluable for Response	Dosed patients who have measurable disease at baseline. Patients will be analysed according to their assigned cohort and planned treatment.
Evaluable for Confirmed Response	Dosed patients with measurable disease at baseline: • who have had the opportunity for ≥2 on-treatment RECIST scans (i.e., patients have been dosed for at least 12 weeks) or • who discontinued from the study or withdrawn from study treatment at the time of data cut-off, and were dosed for less than 12 weeks. This population will only be used for interim analyses. Patients will be analysed according to their assigned cohort and planned treatment.
Pharmacokinetics Analysis Set (PKAS)	All patients who provide concentration data for the study. Patients will be analysed according to the treatment they actually received.

Notes: Analysis set will be defined as above and subset for the TFLs will be applied according to whether they are part of the primary or the re-allocated cohort.
Analysis Set will be defined for re-allocated subjects according to whether they took at least 1 dose of study drug after re-allocation to that module.

*In the absence of complete exposure data relating to dosing on day 1, if the drug accountability data indicate that study drug was taken, it will be assumed that day 1 occurred on the date the study drug was dispensed. Such cases should be included in safety analysis set. However total treatment duration, actual treatment duration and RDI as described in Section 6.5.1 will not be calculated for such cases.

8.4 Demographic and Baseline Characteristics

8.4.1 Demographics

Demographics including age, sex, ethnicity, race and country will be summarised by cohort and module-specific total for ITT, and total for Screen Failures. A list of patient demographics will be provided for the ITT population and Screen failures.

The number of patients in each country and centre will be summarised for ITT.

8.4.2 Baseline Characteristics

Baseline characteristics, biomarker data, disease characteristics and extent of disease will be summarised by cohort and module-specific total for the ITT population.

Baseline characteristics will include the following:

- Height, weight and Body Mass Index
- ECOG performance status
- Pathology of non-small cell lung cancer at baseline: histology type
- Platinum sensitivity (≤ 3 months, >3 - 6 months, >6 - 12 months, >12 - 18 months, ≥ 18 months)
- Time from diagnosis to enrolment (calculated as (Date of pre-screening informed consent - Date of disease diagnosis +1))
- Overall disease classification (locally advanced or metastatic. Metastatic disease includes any patient that has any metastatic site of disease and locally advanced disease includes patient who has only locally advanced sites of disease)
- Number of metastatic sites (0, 1, 2, >=3)
- Extent of disease at study entry will include
    - Summary of extent of disease (Locally advanced, Metastatic)
    - Mean number of target and non target lesions at study entry
    - Mean sum of diameters of target lesions at study entry
- Primary tumour location and tumour, nodes and metastases (TNM) classification at baseline will include summary of the TNM codes for primary tumour in the lung, regional lymph nodes and distant metastases.
- Time in days from most recent disease progression to date of first dose of study drug (calculated as (Date of first dose of study drug - Date of most recent progression +1)).
- Prior immunotherapy, immediate prior immunotherapy and immediate prior platinum-based anti-cancer therapy.

  A prior therapy is defined as a regimen administered prior to dosing with study drug. An immediate prior therapy is defined as the last regimen administered prior to dosing with study drug.

  A subject received immediate prior immunotherapy if the last treatment they received prior to dosing in HUDSON was immunotherapy. A subject received immediate prior platinum-based anti-cancer therapy if the last treatment they received prior to dosing in HUDSON was platinum-based anti-cancer therapy.

- Time in days from last prior immunotherapy to date of first dose of study drug (calculated as (Date of first dose of study drug - Stop date of last prior immunotherapy agent + 1)).
- Duration in days on last prior immunotherapy (calculated as (Stop date of last prior immunotherapy agent – Start date of last prior immunotherapy agent + 1)).
- Time in days from immediate prior immunotherapy to date of first dose of study drug (calculated as (Date of first dose of study drug - Stop date of immediate prior immunotherapy agent + 1)).
- Duration in days on immediate prior immunotherapy (calculated as (Stop date of immediate prior immunotherapy agent – Start date of immediate prior immunotherapy agent + 1)).
- Time to progression on immediate prior immunotherapy (calculated as (Date of progression - Start date of immediate prior immunotherapy agent + 1)).
- Duration in days for immediate prior platinum-based anti-cancer therapy (calculated as (Stop date of immediate prior platinum-based anti-cancer therapy – Start date of immediate prior platinum-based anti-cancer therapy + 1)).
- Time to progression on immediate prior platinum-based anti-cancer therapy (calculated as (Date of progression – Start date of immediate prior platinum-based anti-cancer therapy + 1)).
- Number of prior lines of therapy including number of prior regimens, number of prior immunotherapies, number of prior platinum-based anti-cancer therapies.

In case there are multiple lines of therapies, the time in days and duration in days will be computed for each line of therapy. For the time to progression, the latest of the prior therapies will be considered.

- PD-L1 result (positive, negative, unknown)
- Prior response to an anti-PD-1/PD-L1 containing therapy, or patient resistance (primary resistance, acquired resistance, unknown) as assessed by investigator in eCRF.
- Substance use (tobacco).

  The duration of substance use (years) will be calculated for current and former users as below:

  Current smokers: (current year of the substance use – start year of substance use) + 1.

  Former smokers: (stop year of substance use – start year of substance use) + 1.

In case there are multiple smoking periods, all the periods should be taken into account in the calculation. In case calculation is not possible, but smoking duration was collected from eCRF, then the eCRF values will be kept.

Additional baseline characteristics can also be found further down in Section 8.5.2.

Extent of disease, pathology of non-small cell lung cancer, disease characteristics and substance use will be listed for ITT.

CCI [redacted]

The summary and listing of below baseline characteristics will be provided for screen failures also.

- Disease characteristics (including extent of disease and pathology of non-small cell lung cancer)
- Tumour biomarker profile
- Extent of disease (Listing only)
- Pathology of non-small cell lung cancer (Listing only)

8.4.3 Medical History

Medical and surgical history will be summarised by cohort and module-specific total for ITT. The number and percentage of patients with a medical history, and surgical history, including both resolved and ongoing conditions at the time of study entry, will be summarised by primary system organ class (SOC) and preferred term (PT) in accordance with the medical dictionary for regulatory activities (MedDRA) version 23.0 or higher. Patients will only be counted once per MedDRA level and both medical history and surgical history will be sorted alphabetically by SOC and PT. The details of medical history and surgical history will be listed for ITT.

8.5 Concomitant Medication

The following summaries of medications in this section will be presented by cohort and module-specific total for ITT. All medications will be coded according to the World Health Organization Drug Dictionary Enhanced and Herbal Dictionary (WHO-DDE + HD) 2017Jun B3 format or later version.

8.5.1 Concomitant Medications

For the purpose of the analysis, medications will be classified as either prior, or concomitant (but not both) or post treatment according to its start and stop dates relative to dosing of the study drug in the first cohort.

Prior medication

Prior medication is defined as any medication with a stop date prior to the first dose of any study drug (exclusive).

Concomitant medication

Concomitant medication is defined as any medication with a stop date on or after the first dose of any study drug but before last dose of any study drug, or any medication that is ongoing.

Post treatment medication

Post treatment medication is defined as any medication which started after the last dose of any study drug.

The imputation method described in Section 7.3 will be used in case of medication stop date partially missing. Completely missing stop date will not be imputed and medication will be classified as concomitant.

Note that CSP definition of concomitant medication or eCRF question "Taken prior to study?" will not be used to classify a medication as either prior or concomitant.

Concomitant and post treatment medications will be summarised by Anatomical Therapeutic Chemical (ATC) category name (ATC level 4 or the highest level available i.e. if ATC level 4 is missing, use ATC level 3 and so forth), and generic term (preferred term) for ITT.

Concomitant medications and concomitant procedures will be listed for ITT.

8.5.2 Previous and Subsequent Cancer Treatment

Previous disease-related treatment modalities will summarise previous surgery, radiotherapy immunotherapy and other systemic anti-cancer therapy for ITT and screen failures. Previous disease-related systemic anti-cancer treatment and immediate prior disease-related systemic anti-cancer treatment will be summarised by generic term (preferred term) for the screen failures and ITT analysis sets, respectively.

Number of prior lines of systemic anti-cancer therapy will be a patient's maximum regimen number in prior systemic anti-cancer therapy. Number of prior lines will be summarised as ordinal categories and as a continuous value for ITT.

The immediate prior disease-related systemic anti-cancer therapy is defined as the last regimen administered prior to dosing with study drug. The immediate prior disease-related systemic anti-cancer therapy will be summarised by generic term (preferred term) for ITT.

Listings for prior and subsequent systemic anti-cancer therapy will be provided, and subsequent systemic anti-cancer therapy will also be summarised, for ITT. A listing for previous and subsequent radiation therapy will be provided for ITT.

The prior anti-cancer therapy and prior radiotherapy will be listed for screen failures also.

8.6 Analysis of Efficacy

Efficacy endpoints for tumour response: ORR (BoR), OS, DCR at 12 weeks and 24 weeks, target lesion size and best percentage change from baseline in tumour size, DoR, PFS, CCI [redacted] will be analysed (as summarised in Table 13: Summary of Efficacy Endpoints) by module and cohort, and where appropriate, by module. Note: efficacy data for Module 4 will not be summarised or listed.

The tumour assessment details will be listed and includes the below:

a. Target lesion details
b. Target lesion visit response
c. Non-Target lesion details and visit response
d. New lesion details
e. Investigator overall visit response
f. Calculated overall response and best overall response

Table 13: Summary of Efficacy Endpoints

Efficacy Endpoint	Analysis	Standard RECIST 1.1
ORR	Descriptive statistics including proportion and 80% CI	Yes
BoR	Descriptive statistics	Yes
OS	Descriptive statistics including Kaplan Meier point estimate of median, Q1 and Q3 OS time and 80% CI	NA
DCR	Descriptive statistics including proportion and 80% CI	Yes
Target lesion size	Descriptive statistics	Yes

Sponsor:	AstraZeneca	Protocol/CIP Number:	D6185C00001/Multiple drugs
CIL Project Number:	40773		

Efficacy Endpoint	Analysis	Standard RECIST 1.1
Best percentage change from baseline in tumour size	Descriptive statistics including mean and 80% CI	Yes
DoR	Descriptive statistics including Kaplan Meier point estimate of median, Q1 and Q3 DoR	Yes
PFS	Descriptive statistics including Kaplan Meier point estimate of median, Q1 and Q3 PFS time and 80% CI	Yes
CCI [redacted]		

NA: Not Applicable

Patients in the biomarker matched cohort (Group A) will be summarised by the test result category (only for ORR, BOR, OS, DCR, DoR and PFS):

- Qualifying biomarker = detected AND
  - Exclusion biomarker = not detected
  - Exclusion biomarker = detected
  - Exclusion biomarker = Total
- Qualifying biomarker = not detected
- Central test result unknown
- Overall total

Patients in the biomarker non-matched cohort (Group B) will be summarised by the test result category (only for ORR, BOR, OS, DCR, DoR and PFS):

- Exclusion biomarker = not detected
- Exclusion biomarker = detected
- Overall Total (also includes exclusion biomarker = unknown)

Patients from Module 10 in Group C will be summarised by dose group and by whether they have primary resistance or acquired resistance to prior immunotherapy (based on resistance assessed by investigator in eCRF):

- 160 mg BD
  - Primary
  - Acquired

- Overall total

- 240 mg BD
  - Primary
  - Acquired
  - Overall total

Patients from Module 11 in Group C will be summarised by whether they have primary resistance or acquired resistance to prior immunotherapy (based on resistance assessed by investigator in eCRF):

- Primary
- Acquired
- Overall total

8.6.1 Analysis of Primary Efficacy Variable

The following analyses will be summarised for the Evaluable for Response analysis set.

- Number of patients with an objective response and the ORR (primary efficacy variable) with 80% Clopper Pearson CI.

A description of the number and percentage of patients with categories of BoR (RECIST 1.1) will be provided. The categorisation of BoR will be based on RECIST using the following response categories: CR, PR, SD, PD and NE. Details of BoR will be listed.

Analysis of ORR and BoR will be summarised for the Evaluable for Confirmed Response analysis set for interim analysis only.

8.6.2 Analysis of Secondary Efficacy Variables

8.6.2.1 Overall Survival (OS)

OS will be listed and summarised for ITT (secondary efficacy analysis) and Screen Failures. Descriptive analyses of number of deaths and premature censorings, and duration of follow-up will be performed.

Kaplan Meier (KM) estimates including two-sided 80% CI (using Greenwood's variance and loglog transform approach) will be provided for the median, Q1 and Q3 OS time, the OS rate at 3, 6, 9 and 12 months, and KM plots of OS will be produced for each module stratified by cohort and across all cohorts in each module.

For the interim analysis, along with 80% CI, 60% CI (using Greenwood's variance and loglog transform approach) for the OS rate at 3, 6, 9 and 12 months for each module stratified by cohort will be provided.

For all screen failure patients, enrolled before protocol version 10.0, OS (calculated from the date of consent to the date of death) will be summarised (n, deaths, medians, quartiles, proportion surviving at 3, 6, 9 and 12 months) overall and Kaplan-Meier plots will be presented. Kaplan Meier (KM) estimates including two-sided 80% CI (using Greenwood's variance and loglog transform approach) will be provided for the median.

8.6.2.2 Disease Control Rate (DCR)

The number (%) of patients with disease control at 12 weeks (for RECIST 1.1 variables) will be reported along with 80% Clopper Pearson CI for the Evaluable for Response and Evaluable for Confirmed Response analysis sets by cohort.

The number (%) of patients with disease control at 24 weeks (for RECIST 1.1 variables) will be reported along with 80% Clopper Pearson CI for the Evaluable for Response and Evaluable for Confirmed Response analysis sets by cohort. The Evaluable for Confirmed Response analysis set will be used for interim analysis only.

Disease control rate details will be listed. A swimmer plot for each module stratified by cohort of individual patients' CCI [redacted] will be provided for the Evaluable for Response analysis set.

8.6.2.3 Target Lesion (TL) size

The absolute values TL size, and percentage change in TL lesion size from baseline will be summarised using descriptive statistics and presented at each timepoint and by each cohort for the Evaluable for Response analysis set.

Spider plots showing the percentage change from baseline in TL tumour size and showing the sum of diameters of TL will be presented for each module stratified for the Evaluable for Response and the Evaluable for Confirmed Response analysis sets by cohort. The Evaluable for Confirmed Response analysis set will be used for interim analysis only.

8.6.2.4 Best Percentage Change from Baseline in TL Tumour Size

Best percentage change from baseline in TL tumour size during the study period and 80% t-distribution CI will be presented for the Evaluable for Response analysis set. In addition to the above, the proportion of patients with a reduction from baseline along with 80% CI (using Clopper-Pearson method) will be presented.

Waterfall plots depicting the best percentage change from baseline in TL tumour size will be produced for the Evaluable for Response and the Evaluable for Confirmed Response analysis sets

for each cohort. The Evaluable for Confirmed Response analysis set will be used for interim analysis only.

8.6.2.5 Duration of Response (DoR)

The number of responders and number of responders who subsequently progressed or died will be provided for the Evaluable for Response analysis set.

If there are sufficient numbers of responders, and a sufficient number of responses that have progressed by the point of the analysis, Kaplan Meier (KM) estimates of median, Q1 and Q3 DoR, for each module stratified by cohort will be provided for the Evaluable for Response and Evaluable for Confirmed Response analysis sets. If number of responders per cohort was less than 3, the quartiles of the duration of response will not be not calculated. The Evaluable for Confirmed Response set will be used for interim analysis only.

In addition, DoR will be listed and swimmer plot of individual patients' DoR for each module stratified by cohort will be provided for the Evaluable for Response analysis set and for the Evaluable for Confirmed Response analysis set.

8.6.2.6 Progression-Free Survival (PFS)

PFS will be listed and summarised for ITT. Descriptive analyses of number of progression events and premature censorings, and duration of follow-up will be performed.

KM estimates including two-sided 80% CI (using Greenwood's variance and loglog transform approach) will be provided for the median, Q1 and Q3 PFS time, the PFS rate at 3, 6, 9 and 12 months, and KM plots of PFS will be produced for each module stratified by cohort and across all cohorts in each module.

For the interim analysis, along with 80% CI, 60% CI (using Greenwood's variance and loglog transform approach) for the PFS rate at 3, 6, 9 and 12 months for each module stratified by cohort will be provided.

8.6.2.7 New Lesions

A summary of patients with and without new lesions will be presented by frequency counts and percentages. CCI [redacted] The number of new lesions will be summarised for the categories- 1 lesion, 2 lesions, 3 lesions, 4 lesions, 5 lesions and >5 lesions. Summaries will be presented for ITT.

An additional table to summarise new lesions per visit will be presented. This summary will include number of patients with new lesions, new lesions that significantly worsened and new lesions that disappeared along with the site of new lesion.

8.6.2.8 Other Efficacy Analysis

The number and percentage of patients who received further therapy for cancer and who did not receive further therapy for cancer relative to progression after study treatment will be presented for ITT analysis set. When more than one cancer therapy after treatment is collected, only the first will be summarised.

In addition, CCI [redacted] summarising number of patients requiring subsequent cancer therapy and treatment regimen will be presented for ITT analysis set and screen failures.

A listing of CCI [redacted] will be provided for ITT analysis set and screen failures.

8.7 Analysis of Safety

Safety variables including extent of exposure and compliance, adverse events, laboratory tests, vital signs, ECG and other safety measurements will be summarised by cohort and module-specific total for the SAF.

8.7.1 Exposure

Summaries of duration of exposure to individual drugs, RDI, and dose interruptions, delays and reductions will be provided by study drug and based on the SAF.

For the study drugs which are administered in cycles, a summary will be presented with descriptive statistics for number of cycles and frequency counts and percentages with categories for number of cycles (≥1 cycle, ≥2 cycles, ≥3 cycles etc.).

Further the dose modification will be summarised with frequency count and percentages which includes number of patients and reasons for the below:

- Dose reduction (non-durvalumab drugs)
- Dose modification (non-durvalumab drugs)
- Dose delay (durvalumab, AZD9150, oleclumab, trastuzumab deruxtecan).
- Dose interruptions (all study drugs)

The time to first delay and time to first interruption will summarised descriptively with number of patients with delay/interruption, median, min and max.
The exposure to each of the study drugs will be listed. Any incidences of overdose will be listed.

8.7.2 Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary 23.0 or higher. Toxicity will be graded according to the NCI CTCAE v4.03.

Key guidelines for counting incidence proportions of adverse events are as follows:

1. When a patient has the same AE reported multiple times during an analysis period based on System Organ Class (SOC) and preferred term (PT), the patient will only be counted once within a level of MedDRA in an AE incidence table.
2. When assessing investigator reported relationship to study drug of the AEs, if an AE changes in causal relationship during an analysis period for a patient, the related event will be chosen.
3. When summarising intensity of the AEs, if an AE changes in CTCAE grade during an analysis period for a patient, the AE with the maximum CTCAE grade will be chosen. In case the AE term (SOC and PT) is reported more than once, one of them with missing grade, and at least another with non-missing grade, the maximum CTCAE grade will be chosen from the non-missing grade values and the missing grade can be ignored. If all are of missing grade, then the AE severity will be summarised in an additional "Unknown" intensity category.
4. When summarising intensity for drug-related AEs, only drug related AEs will be used in the analysis. If a patient has the same AE reported multiple times during an analysis period for a drug-related AE, the AE with the maximum CTCAE grade will be chosen.
5. Several actions taken with study treatment can be entered in AE page and AE change forms. Each action taken will be flagged and count in summary tables, however in listing only the worst value will be presented considering the following severity order (worst to less severe): drug withdrawn, drug interrupted, dose reduced, dose not changed, NA, blank.

An overview of TEAEs will be summarised at the patient and episode levels for SAF for the following

- Any AE
- Any AE with causal relationship to study drugs
- Any AE related to study procedure
- Any AE with CTCAE grade ≥ 3
- Any AE with outcome of death,
- Any SAE
- Any SAE with outcome of death
- Any AE leading to discontinuation of study drugs
- Any AE leading to discontinuation with causal relationship to study drugs
- Any AE leading to dose interruption
- Any AE leading to dose reduction (non-durvalumab drugs)

- Any AE leading to dose modification (non-durvalumab drugs)
- Any AE leading to dose delay (IV drugs)
- Any AE of special interest (durvalumab, olaparib, oleclumab, trastuzumab deruxtecan, cediranib)
- Any imAE for durvalumab

Summaries of patients with TEAEs classified by SOC and PT will be provided for SAF. The summary of patients with TEAEs will also be repeated for:

- TEAEs causally related to any study drug, for each study drug and for both study drugs
- TEAEs by maximum CTCAE grade
- TEAEs causally related to any study drug, for each study drug and for both study drugs by maximum CTCAE grade
- TEAEs for CTCAE grade ≥3
- TEAEs causally related to any study drug, for each study drug and for both study drugs, adverse events of CTCAE grade 3 or higher
- TEAEs leading to dose interruption of each study drug
- TEAEs leading to dose delay of each study drug where applicable
- TEAEs leading to dose reduction of each study drug where applicable
- TEAEs with outcome of death
- TEAEs causally related to any study drug, for each study drug and for both study drugs with outcome of death
- Serious TEAEs
- Serious TEAEs causally related to any study drug, for each study drug and for both study drugs
- Non-serious TEAEs occurring in greater than 5% of patients (Number of events along with number (%) of patients. Incidence of 5% will be considered as per the modular total incidence.)
- Serious TEAEs with outcome of death
- Serious TEAEs causally related to any study drug, for each study drug and for both study drugs with outcome of death.

- Serious TEAEs by maximum CTCAE grade
- Serious TEAEs by maximum CTCAE grade - causally related to any study drug, for each study drug and for both study drugs
- TEAEs leading to discontinuation of each study drug and for both study drugs.
- TEAEs causally related leading to discontinuation of each study drug and for both study drugs
- Infusion Related TEAEs

In addition, the number of TEAEs and number of serious TEAEs classified by SOC and PT will be provided for SAF.

The key patient information listings will be provided for the following-

- TEAEs with outcome of death
- Serious TEAEs
- TEAEs leading to discontinuation of study treatment.

TEAEs of special interest to each study drug will be summarised by

- AESI and preferred term
- AE of special interest and maximum CTCAE grade.

An overview of AESI/AEPI/imAE for durvalumab will be summarised at the subject levels and it will be summarised by

- AESI category and subcategory
- AESI category and subcategory by maximum CTCAE grade
- AESI category and preferred term
- AESI category and preferred term by maximum CTCAE grade
- AESI category and time to onset
- AESI category and duration of high steroid
- AESI category and outcome
- AESI category and subcategory and preferred term
- AESI category and subcategory and preferred term by outcome
- AESI category and preferred term by event rate

AESI category and preferred and maximum reported CTCAE grade

Category and subcategory for AESI could be a group of HLT, SOC or PT depending the team decision.

The following listings will be presented

- All AEs,
- All SAEs
- All deaths
- Procedure related adverse events including 21 days after tumour biopsy procedure
- All AEs occurring prior to the first dose of any study drug
- All AEs after the 90-day follow-up period will be listed for SAF (for re-allocated subjects, also includes adverse events with onset during the defined 90-day follow-up period after discontinuation of study drug from the first cohort for which the investigator assessed the relatedness of the AE to the non-durvalumab study drug from the second cohort)
- PTs defining TEAE of special interest
- AE for subjects with confirmed/suspected COVID-19 infection
- All AESI and AEPI for durvalumab
- Time to and duration of systemic steroids for imAE for durvalumab

Time to onset/resolution of imAE for durvalumabFor Screen Failures, AEs and SAEs will be listed along with summaries of patients with AEs and number of adverse events classified by SOC and PT.

Note that the infusion related/hypersensitivity reactions AESI will not be presented in any of the AESI/AEPI/imAE specific outputs.

8.7.2.1 Type of Death

The following criteria will be used to construct categories for deaths:

- Whether they occur within the treatment-emergent adverse event period (from first dose of any study drug) up to ≤90 days after last dose of study drug) or occur >90 days after last dose of study drug, and
- For deaths occurring within the treatment emergent period, whether they are related to the disease under investigation and/or are AEs with outcome of death (serious TEAE).

Sponsor:	AstraZeneca	Protocol/CIP Number:	D6185C00001/Multiple drugs
CIL Project Number:	40773		

Mutually exclusive categories for death are defined in Table 14. The number and percentage of deaths of each category and total number of deaths will be summarised for SAF. All deaths will be listed and include all deaths up to/including the DCO for the module.

Table 14: Mutually Exclusive Categories for Death

Mutually exclusive categories for death	Death related to disease under investigation	Death related AE	Additional Information
Death related to disease under investigation only	Yes	No	
AE with outcome of death only	No	Yes	Includes adverse events with an onset date or worsening in CTCAE grade on or after the date of first dose of any study drug and up to and including 90 days following the date of last dose of study drug. For the re-allocated subjects, includes AEs that started or worsened in CTCAE grade on or after the first dose of any study drug from the first cohort, until 90 days follow-up after discontinuation of study drug from the first cohort, unless the investigator assessed the relatedness of the AE with onset during this interval to the non-durvalumab study drug from the second cohort. For patients in Module 11 who went on to receive durvalumab + ceralasertib combination therapy as subsequent therapy, includes AE that started or worsened in CTCAE grade on or after the first dose of ceralasertib monotherapy, until 90 days follow-up after discontinuation of ceralasertib monotherapy, unless the investigator assesses the AE with onset during this interval to be related to ceralasertib or durvalumab and the AE started after initiation of durvalumab.
AE with outcome of death only (AE start date falling after 90 day follow up period)	No	Yes	For the re-allocated subjects, includes AEs that started or worsened up to 90 days follow-up after discontinuation of study drug from the first cohort if the

Mutually exclusive categories for death	Death related to disease under investigation	Death related AE	Additional Information
			investigator assessed the relatedness of the AE with onset during this interval to the non-durvalumab study drug from the second cohort. For patients in Module 11 who went on to receive durvalumab + ceralasertib combination therapy as subsequent therapy, includes AE that started or worsened in the 90 days follow-up after discontinuation of ceralasertib monotherapy if the investigator assesses the AE with onset during this interval to be related to ceralasertib or durvalumab and the AE started after initiation of durvalumab.
Death related to disease AND an AE with outcome of death	Yes	Yes	Only AEs from first period
Other deaths not captured in categories of deaths related to disease under investigation or AE with outcome of death	No	No	

8.7.2.2 Dose Limiting Toxicity (DLT) for Module 6 only

The dose limiting toxicity will be summarised and listed by cohort with number of evaluable patients, number of evaluable patients with a DLT along with MedDRA and CTCAE grade using SAF.

8.7.2.3 Clinical Laboratory Evaluations

8.7.2.3.1 Safety Laboratory Tests

All summaries will be reported in international System of units (SI). Haematology, clinical chemistry and coagulation parameters are continuous variables. Urinalysis parameters are categorical variables except specific gravity and pH.

Absolute value, change from baseline and percentage change from baseline for continuous data for haematology, clinical chemistry and coagulation will be presented by analysis visit for SAF. The descriptive summary includes n, mean, geometric mean (geomean), SD, median, Q1, Q3, minimum and maximum for actual values, and n, mean, SD, median, Q1, Q3, minimum and maximum (not geomean) for change from baseline and percentage change from baseline. If one or more values for

a given parameter is zero, then no geometric statistics will be calculated for that parameter and the results for geometric statistics will be set to NA (Not Applicable).

Where appropriate, haematology, clinical chemistry and coagulation parameters will be log-transformed. A summary table will be presented for the ratios post-baseline/baseline calculated by log-transforming the baseline and post-baseline results, and then back-transforming the summary statistics:

- Ratio from post-baseline to baseline (%) will be defined as the exponent of the logarithm of the visit value minus the logarithm of the baseline value.

Haematology, clinical chemistry, and coagulation values will be classified as low (L), normal, and high (H) according to the normal ranges. In addition, CTCAE grading (NCI CTCAE v4.03) taking values Grade 1, 2, 3, or 4, will be used to classify selected haematology, clinical chemistry and coagulation parameters that deviate above or below the normal range. The list of selected parameters is provided in Table 10.

Lab parameters with CTCAE grading will be summarised in shift tables comparing maximum CTCAE grade at post-baseline with those at the baseline visit. The percentage of patients in the shift table will be based on the number of patients with a baseline and at least one post baseline value on treatment.

Box plots by analysis visit will be presented for absolute values and change from baseline of haematology, clinical chemistry and coagulation parameters by cohort and module-specific total. A line inside the box will present the median, the box range will be Q1 to Q3, whiskers should extend to the most extreme observations within 1.5IQR from the nearest quartile and the outliers which are out of 1.5 interquartile range (IQR) will be plotted.

Urinalysis data will not be summarised. All laboratory results will be presented in listings for SAF. The clinical significance of the laboratory results (Yes/No) will be included in the listings for the data reported by local labs only.

8.7.2.3.2 Hy's Law Laboratory Evaluations

Potential Hy's Law (PHL) is defined as having the following combination of values:

(aspartate aminotransferase (AST) **or** alanine aminotransferase (ALT) ≥3 x upper limit of normal (ULN) **and** total bilirubin (TBL) ≥2 x ULN)

at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

Hy's Law (HL) is defined as having the following combination of values:

(AST **or** ALT ≥3 x ULN **and** TBL ≥2 x ULN)

where no other reason, other than the study drug, can be found to explain the combination of increases, e.g. elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (i.e. on the same day) the elevation in TBL, but there is no specified time frame within which the elevations in transaminases and TBL must occur.

For patients with ALT or AST ≥3 x ULN and TBL ≥2 x ULN, their ALT, AST and total bilirubin data will be listed along with ALP and GGT. The subjects who have ALT or AST≥3xULN and total bilirubin ≥2xULN, and the elevation in transaminases precede or coincide with (that is, on the same day as) the elevation in TBL will be included in this listing.

The liver assessments, liver risk factors, liver signs and symptoms for patients with potential Hy's law in the investigator opinion will be listed using SAF.

Scatter plots on log-log scale of the maximum value on treatment total bilirubin in xULN versus ALT (xULN) and AST (xULN) will be provided by cohort and module-specific total, for SAF. Note: Plotted maxima need not be concurrent, i.e. a patient may not have had the maximum ALT at the same time as his maximum total bilirubin.

A line plot of liver biochemistry test results (ALT, AST, TBL, ALP and GGT) in units of xULN on log scale versus actual time in study days will be plotted for individual patients who meet the potential Hy's Law criteria. This figure will be produced only for those patients with potential Drug Induced Liver Injury (i.e. ALT/AST ≥ 3*ULN and TBL ≥ 2*ULN and in which the elevation in transaminases precede or coincide with (that is, on the same day as) the elevation in TBL).

8.7.2.3.3 Pregnancy

A listing of positive pregnancy results for female patients of childbearing potential only will be provided for SAF.

8.7.3 Other Observations Related to Safety

8.7.3.1 ECG

Absolute value and change from baseline for ECG data will be presented by analysis visit for SAF. QTcF prolongation criteria at any time during treatment will be summarised for SAF. Box plots by analysis visit will be presented for absolute values and change from baseline of ECG parameters by cohort and module-specific total. All ECG continuous data and ECG findings will be presented in listings for SAF.

8.7.3.2 Vital Signs

Absolute value and change from baseline for vital signs will be presented by analysis visit for SAF. Additional time points will be presented for blood pressure and pulse rate as described in Section 6.5.4.1.

Box plots by analysis visit will be presented for absolute values and change from baseline of vital signs parameters by cohort and module-specific total for SAF. All vital signs data will be presented in listings for SAF.

In summary tables, only data selected according to visit windows (Section 6.2.3) defined by the visits scheduled in the protocol will be presented. All data will be listed.

8.7.3.2.1 Oxygen Saturation

For Module 6, absolute value and change from baseline for SpO_2 will be presented by analysis visit for SAF.

SpO_2 data recorded for all modules will also be presented in listings. Oxygen saturation pre and post dose, pulmonary function test will be presented in listings.

8.7.3.2.2 Additional Vital Signs Measurements Recorded by Patients (Module 7 only)

Definition of Week and Month:

A week is defined as a block of 7 consecutive days, and where the first block starts with Day 1 (D1).

A month is defined as a block of 28 consecutive days, and where the first block starts with Day 57 (D57).

Hypertension and Hypotension:

Hypertension: BP measurements will be flagged as hypertension if either systolic blood pressure (SBP)≥140 mmHg and/or diastolic blood pressure (DBP)≥90 mmHg.

Hypotension: BP measurements will be flagged as hypotension if there is a drop from baseline SBP (as measured by the site) of ≥20 mmHg and/or a drop from baseline DBP of ≥10 mmHg.

Persistent hypertension (i.e episode of hypertension lasting more than 24 h) will be defined as a hypertension event on at least 2 consecutive days in the same time period (morning/evening). Persistent hypotension is defined similarly.

Hypertension, grade 3 hypertension, hypotension, persistent hypertension/hypotension will be derived based on morning and evening averages as defined in 6.5.4.1.2.

Sponsor:	AstraZeneca	Protocol/CIP Number:	D6185C00001/Multiple drugs
CIL Project Number:	40773		

All patients will be checked for the occurrence of hypertension and hypotension during the study and summarised for the timepoints Week 1, Week 2, …. Week 8, Month 3, Month 4 and so on.

If a patient had their first hypertension event in the timepoints mentioned above, then the total number of hypertension events the patient had during the study will be summarised as per the categories mentioned below.

- 1 event
- 2 events
- 4-6 events
- 7-9 events
- ≥10 events

If a patient has 1 or 2 hypertension events on the same day, then it will be counted as 1 to the total number of events. (The summary will be of the total number of days the patient had at least one hypertension event.)

Similar analysis will be carried out for the patients reporting hypotension also.

The additional BP data will be summarised using SAF. A summary table of hypertension will be presented summarising below:

- Number of patients with at least one hypertension event
- Number of patients with their first hypertension event in each timepoints (Week 1, Week 2…. Week 8, Month 3, Month 4, ….)
- Number of hypertension events the patients had during the study for patients who had their first hypertension event during the timepoint being presented

If no patient had their first hypertension event during a particular timepoint window, then that timepoint will not be presented.

A similar summary of hypotension events will be presented.

The additional BP measurements along the average AM/PM measurements will be presented in listing. The BP device also records pulse rate, and these will also be listed.

No plots will be presented for these additional BP measurements.

8.7.3.3 Physical Examination

Listings of screening (baseline) and targeted (post-baseline) physical examination findings will be provided for SAF.

8.7.3.4 ECOG Performance Status

Listings of ECOG status will be provided for SAF.

8.7.3.5 Ophthalmology (Module 6 only)

Visual Acuity

Absolute value and change from baseline at study drug discontinuation visit for visual acuity be presented by analysis visit for SAF.
The above summary will be presented for

- ETDRS score
- Snellen's or Landolt's scores converted to decimals

The details of visual assessments will be listed individually by patient within the SAF.

Slit lamp Examination and Fundoscopy

Shift from baseline at 28 days after study discontinuation in abnormality of slit lamp examination and fundoscopy will be summarised with frequency counts and percentages for SAF. The categories to be summarised are:

- Normal
- Abnormal, not clinically significant
- Abnormal, clinically significant

8.7.3.6 LVEF (Module 6 and 7 only)

The observed value and change from baseline will be presented for LVEF assessment by analysis visit using SAF. The details of LVEF assessments will be listed individually by patient.

Shift from baseline in normal/borderline/abnormal condition LVEF will be summarised with frequency counts and percentages using SAF.

8.7.3.7 Interstitial Lung Disease (ILD) (Module 6)

All ILD events submitted to the ILD adjudication committee will be summarized by CTCAE grade in the following categories: adjudicated as ILD (adjudicated as study drug-related ILD, adjudicated as not study drug-related ILD), adjudicated as not ILD, unable to adjudicate due to insufficient information. Each patient will be counted only in one category. For patients having ILD events across multiple categories, the patient will be counted in the highest category according to the order

described earlier in this paragraph. If a patient had multiple ILD events, the CTCAE grade will be shown for the event with the worst grade. For events adjudicated as ILD, the CTCAE grade assessed by adjudication committee will be presented and for events unable to adjudicate due to insufficient information the CTCAE grade assessed by investigator will be used. In case of multiple CTCAE grades for an ILD event, the worst CTCAE grade will be used.

A listing will be provided for ILD/pneumonitis using the SAF. The maximum CTCAE grade that is summarized in the tables will be displayed in the listing. This maximum CTCAE grade may differ from the overall maximum CTCAE grade since it is defined to not consider any CTCAE grade that occurred after anti-cancer therapy.

A second listing will be provided for detailing the Interstitial lung disease examination data using the SAF.

8.8 Pharmacokinetics

8.8.1 PK Concentrations for AZD9150, AZD6738, trastuzumab deruxtecan, durvalumab and cediranib

PK concentrations of AZD9150, AZD6738, trastuzumab deruxtecan, durvalumab and cediranib will be listed by respective modules by cohort and dose regimen when applicable for the PK analysis set. Tabular and/or graphical summaries will be generated for PK concentration data from each respective module if appropriate.

8.8.2 Immunogenicity

Durvalumab ADA data will be reported at the end of the study in the core CSR and will summarize data overall (rather than by module).

The number of patients who are confirmed to develop detectable anti-drug antibodies against durvalumab (all modules except modules 8 and 11), AZD9150 (Module 2), and trastuzumab deruxtecan (Module 6) will be summarised by cohort and module-specific total for the SAF.

The immunogenicity analysis will provide the number of patients with an immunogenicity sample, the percentage of patients with a positive sample for the SAF.

A listing will be presented for the ADA samples which were collected for oleclumab prior to protocol amendment v6.0.

8.8.3 Other Exploratory Variables

The details of qualifying and exclusion biomarkers with the specimen details and the results will be listed and summarized for ITT and screen failures. Data from local test and all central laboratories will be used in table and listings.

Summary table on biomarker data at pre-screening will include:

- Summary of qualifying inclusion and exclusion biomarker
- Biomarker profile by patient resistance status (as assessed by investigator in eCRF)
- Biomarker status by central laboratory and local test

9 Computer Software

All analyses will be performed by Labcorp using Version 9.4 of SAS® software. The standard operating procedures (SOPs) of Chiltern will be followed in the creation and quality control of all data displays and analyses.

10 References

- **Austin et al 2015**

Austin, P. C., & Stuart, E. A. (2015). Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. Statistics in Medicine, 34, 3661–3679. https://doi.org/10.1002/sim.6607.

- **Frewer et al 2016**

Frewer P, Mitchell P, Watkins C, Matcham J, et al. Decision-making in early clinical development. Pharm Stat. 2016 May; 15(3):255-63.

- **Rosenbaum et al (1983)**

Rosenbaum, Paul R.; Rubin, Donald B. (1983). "The Central Role of the Propensity Score in Observational Studies for Causal Effects". Biometrika. 70 (1): 41–55. doi:10.1093/biomet/70.1.41.

- Clinical study protocol version 13.0 final, 14Dec2023

11 TABLE SHELLS AND SPECIFICATIONS

ECD Biometrics – HUDSON SAP TOC

Reference document for standards	Version	Date created
AZ Corporate CSRHLD Tables Templates	2.3	January 12, 2018
AZ Corporate CSRHLD Figures Templates	2.1	January 12, 2018
AZ Oncology TA TFL Templates	2.1	July 20, 2016
AZ Oncology TA Appendix 12.2 Listing Templates	2.0	March 5, 2018
Global Specification For Clinical Study Report Appendix 12.2 (Patient Data Listings)	2.2	December 20, 2016
Section 11 TFL Appendix 12 2 Patient Data Listing Numbering Conventions		July 2, 2014
AZ Corporate CSRHLD Reporting Standards	2.3	January 12, 2018
AZ Durvalumab TFL templates		July 9, 2021

Sponsor:	AstraZeneca	Protocol/CIP Number:	D6185C00001/Multiple drugs
CIL Project Number:	40773		

TFL number	Title	Standard	Additional Information	CSR	Every 3 month review	SRC *	Screen failure	IA Modules 10 and 11
				Any module specific outputs are identified as Mx where M: Module and 'x': module number (Ex: M6, M7 etc.). AR: As required. * Prior to CSP v10.0				

14.1 Demographic, baseline, concomitant medication and other patient-specific characteristics

Demographic, baseline, concomitant medication and other patient-specific characteristics	Present each module on a separate page. - Module 1: Cohort A.1.HRR, Cohort A.1. LKB, Cohort B.1.PRI, Cohort B.1.ACQ - Module 2: Cohort B.2.PRI, Cohort B.2.ACQ - Module 3: Cohort A.3.ATM, Cohort B.3.PRI, Cohort B.3.ACQ - Module 4: Cohort A.4.RIC - Module 5: Cohort A.5.73H, Cohort B.5.PRI, Cohort B.5.ACQ - Module 6: Cohort A.6.HER2e, Cohort A.6.HER2m - Module 7: Total - Module 8: Cohort A.8.ATM - Module 9: Cohort B.9.PRI, Cohort B.9.ACQ - Module 10: Cohort C.10.160 (PRI and ACQ), Cohort C.10.240 (PRI and ACQ) - Module 11: Cohort C.11.240 (PRI and ACQ) AZDXXX should be populated with the study drug for that module (Olaparib, AZD9150, AZD6738, Vistusertib, Oleclumab, trastuzumab deruxtecan, Cediranib)

Disposition

Distribution: *Original:* *Copy:*

Table 14.1.1.1	Subject disposition (Enrolled subjects)	TDEM010	For quarterly reviews, table is: Table 11.1.1.1	X	X			
Table 14.1.1.2	Subject disposition (Enrolled subjects with treatment allocation)	TDEM010	For quarterly reviews, table is: Table 11.1.1.2	X	X			
Table 14.1.1.3	Subject disposition (ITT analysis set)	TDEM010	Requested for M11 futility analysis. For quarterly reviews, table is: Table 11.1.1.3	X	X			X
Table 14.1.1.4	Summary of COVID-19 study disruptions (ITT analysis set)	COVID-summary3		X				
Table 14.1.2	Important protocol deviations (ITT analysis set)	SP2	For quarterly reviews, table is: Table 11.1.2	X	X			
Table 14.1.3	Analysis sets	TDEM30	For quarterly reviews, table is: Table 11.1.3	X	X			

Demographic characteristics

Table 14.1.4.1	Demographic characteristics (ITT analysis set)	SP4	Requested for M11 futility analysis. For quarterly reviews, table is: Table 11.1.4.1	X	X			X
Table 14.1.4.2	Demographic characteristics (Screen failures)	SP4	For quarterly reviews, table is: Table 11.1.4.2	X	X		X	

Table 14.1.5	Subject recruitment by country and centre (ITT analysis set)	ASP1		X				
Table 14.1.6	Subject baseline characteristics (ITT analysis set)	SP8	For quarterly reviews, table is: Table 11.1.6	X	X			

Baseline disease characteristics

Table 14.1.7.1	Previous disease-related treatment modalities (ITT analysis set)	TDEM060		X				X
Table 14.1.7.2	Previous disease-related treatment modalities (Screen Failures)	TDEM060		X			X	
Table 14.1.8.1	Previous disease-related systemic anti-cancer treatment (ITT analysis set)	TDEM065		X				
Table 14.1.8.2	Immediate prior disease-related systemic anti-cancer treatment (ITT analysis set)	TDEM065		X				
Table 14.1.8.3	Previous disease-related systemic anti-cancer	TDEM065					X	

	treatment (Screen Failures)							
Table 14.1.9	Number of prior lines of systemic anti-cancer therapy (ITT analysis set)	TDEM070	Requested for M11 futility analysis. For quarterly reviews, table is: Table 11.1.9	X	X			X
Table 14.1.10	Medical history (ITT analysis set)	SP7(i)		X				
Table 14.1.11	Surgical history (ITT analysis set)	SP7(ii)		X				
Table 14.1.12.1	Disease characteristics (ITT analysis set)	TDEM110	Requested for M11 futility analysis. For quarterly reviews, the table is: Table 11.1.12.1 Include only Histology Type, Overall disease classification, ECOG	X	X		X	X
Table 14.1.12.2	Disease characteristics (Screen failures)	TDEM110	For quarterly reviews, the table is: Table 11.1.12.2 Include only Histology Type, Overall disease classification, ECOG.	X	X		X	
Table 14.1.13	Extent of disease at study entry (ITT analysis set)	TDEM130	For quarterly reviews, the table is: Table 11.1.13	X	X			X
Table 14.1.14	Primary tumour location and TNM classification at baseline (ITT analysis set)	TDEM130A	For quarterly reviews, the table is: Table 11.1.14	X	X			
Table 14.1.15	Time from most recent disease progression to	TDEM200		X				

	date of first dose (ITT analysis set)							
Table 14.1.16.1	Duration of last prior immunotherapy and time of last prior immunotherapy relative to first dose (ITT analysis set)	TDEM200		X				
Table 14.1.16.2	Duration of immediate prior immunotherapy and time of immediate prior immunotherapy relative to first dose (ITT analysis set)	NEW1		X				
Table 14.1.16.3	Time to progression on immediate prior immunotherapy (ITT analysis set)	NEW1		X				
Table 14.1.16.4	Duration of immediate prior platinum-based anti-cancer therapy (ITT analysis set)	TDEM200		X				
Table 14.1.16.5	Time to progression on immediate prior platinum-based anti-	NEW2		X				

	cancer therapy (ITT analysis set)							
Table 14.1.17.1	All concomitant medications during study treatment (ITT analysis set)	SP10		X				
Table 14.1.17.2	Post treatment medications (ITT analysis set)	SP10		X				
Table 14.1.18	Substance use (tobacco), categorised (ITT analysis set)	ASP2	For quarterly reviews, the table is: Table 11.1.18	X	X			
Table 14.1.19.1	Summary of qualifying and exclusion biomarkers (ITT analysis set)	NEW3		X				
Table 14.1.19.2	Summary of qualifying and exclusion biomarkers (Screen Failure)	NEW4		X				
Table 14.1.19.3	Stratification factors for cohort allocation (ITT analysis set)	NEW5	Apply only for Modules 1, 3, 5, 6 and 8	X				
Table 14.1.19.4	Biomarker status for cohort allocation (ITT analysis set)	NEW45		X				

Sponsor:	AstraZeneca	Protocol/CIP Number:	D6185C00001/Multiple drugs
CIL Project Number:	40773		

14.2.1 Efficacy

Efficacy	Present each cohort on a separate page. For the biomarker matched cohort (Group A), the efficacy endpoints will be summarised by central test result:
	• Qualifying biomarker = detected, exclusion biomarker = not detected
	• Qualifying biomarker = detected, exclusion biomarker = detected
	• Qualifying biomarker = detected
	• Qualifying biomarker = not detected
	• Qualifying biomarker = unknown
	• Qualifying biomarker = total
	
	For the non-matched cohort (Group B), the efficacy endpoints will be summarised by the response to prior PD1/PDL1 therapy (primary or acquired resistance) and by central test result:
	• Exclusion biomarker = not detected
	• Exclusion biomarker = detected
	• Exclusion biomarker = total
	
	For the group C, the efficacy endpoints will be summarized by dose group and resistance for Module 10:
	• 160 mg BD
	  ○ Primary
	  ○ Acquired
	  ○ Overall total
	• 240 mg BD
	  ○ Primary

	○ Acquired ○ Overall total For Module 11, the efficacy endpoints will be summarized by resistance: • Primary • Acquired • Total

Best Objective Response and Summaries of Response

Efficacy – Best Objective Response and Summaries of Response								
Table 14.2.1.1	Best objective response (Evaluable for response analysis set)	TEFF110NR	For quarterly reviews, the table is: Table 11.2.1.1.1	X	X			
Table 11.2.1.1.2	Best objective response (Evaluable for confirmed response analysis set)	TEFF110NR	For quarterly reviews, futility and interim analyses only. For futility and interim analyses, the table is: Table 14.2.1.1.2.		X			X
Table 14.2.1.2	Objective response rate (Evaluable for response analysis set)	TEFF140	For quarterly reviews, the table is: Table 11.2.1.2.1	X	X			
Table 11.2.1.2.2	Objective response rate (Evaluable for confirmed response analysis set)	TEFF140	For quarterly reviews, futility and interim analyses only. For futility and interim analyses, the table is: Table 14.2.1.2.2.		X			X
Table 14.2.1.3.1	Disease control rate at 12 weeks (Evaluable for response analysis set)	TEFF160	For quarterly reviews, the table is: Table 11.2.1.3.1	X	X			
Table 11.2.1.3.2	Disease control rate at 12 weeks (Evaluable for confirmed response analysis set)	TEFF160	For quarterly reviews and interim analyses only. For		X			X

			interim analyses, the table is: Table 14.2.1.3.3.					
Table 14.2.1.3.2	Disease control rate at 24 weeks (Evaluable for response analysis set)	TEFF160	For quarterly reviews, the table is: Table 11.2.1.3.3	X	X			
Table 11.2.1.3.4	Disease control rate at 24 weeks (Evaluable for confirmed response analysis set)	TEFF160	For quarterly reviews and interim analyses only. For interim analyses, the table is: Table 14.2.1.3.4.		X			X
Table 14.2.1.4.1	Duration of response in subjects with confirmed response (Evaluable for Response analysis set)	TEFF150		X				
Table 11.2.1.4.1	Duration of response in subjects with confirmed response (Evaluable for confirmed response analysis set)	TEFF150	For quarterly reviews and interim analyses only. For interim analyses, the table is: Table 14.2.1.4.1.2		X			X
Figure 14.2.1.4.2	Swimmer plot of the subjects' duration of response (Evaluable for Response analysis set)	ZEFF020_DOR	Alternative presentation for duration of response if too few patients have responded to support production of Kaplan Meier plot ZEFF070.	X				
Figure 11.2.1.4.1	Swimmer plot of the subjects' duration of response (Evaluable for confirmed response analysis set)	ZEFF020_DOR	For quarterly reviews and interim analyses only. For interim analyses, the table is: Figure 14.2.1.4.1.		X			X

Figure 14.2.1.4.3	Swimmer plot of the subjects' CCI [redacted] (Evaluable for Response analysis set)	ZEFF020_DOR	Alternative presentation for duration of response if too few patients have responded to support production of Kaplan Meier plot ZEFF070.	X				

Overall survival

Efficacy – Overall survival								
Table 14.2.1.5.1.1	Overall survival (ITT analysis set)	TEFF280	Requested for M11 futility analysis. For quarterly reviews, the table is: Table 11.2.1.5.1	X	X			X
Table 14.2.1.5.1.2	Overall survival summary for module (ITT analysis set)	TEFF280		X				
Table 14.2.1.5.2	Overall survival (Screen failure subjects)	TEFF280	For quarterly reviews, the table is: Table 11.2.1.5.2	X	X		X	
Figure 14.2.1.5.3	Overall survival, Kaplan Meier plot (ITT analysis set)	ZEFF070	Requested for M11 futility analysis. For quarterly reviews, the table is: Figure 11.2.1.5.1	X	X			X

Figure 14.2.1.5.4	Overall survival, Kaplan Meier plot (Screen failure subjects)	ZEFF070	For quarterly reviews, the table is: Figure 11.2.1.5.2	X	X		X	
Figure 14.2.1.5.5	Overall survival, Kaplan Meier plot for all ITT subjects (ITT analysis set)	ZEFF070		X				

Progression-free survival

Efficacy – Progression-free survival								
Table 14.2.1.6.1.1	Progression-free survival (ITT analysis set)	TEFF010	Requested for M11 futility analysis. For quarterly reviews, the table is: Table 11.2.1.6.1	X	X			X
Table 14.2.1.6.1.2	Progression-free survival summary for module (ITT analysis set)	TEFF010		X				
Figure 14.2.1.6.2	Progression-free survival, Kaplan Meier plot (ITT analysis set)	ZEFF070	Requested for M11 futility analysis. For quarterly reviews, the figure is: Figure 11.2.1.6.1	X	X			X
Figure 14.2.1.6.3	Progression-free survival, Kaplan Meier plot for all ITT subjects (ITT analysis set)	ZEFF070		X				

Target lesions

Efficacy – Target lesions								
Table 14.2.1.7.1	Target lesion size, percentage change from baseline (Evaluable for response analysis set)	TEFF200		X				
Figure 14.2.1.7.2	Spider plot showing the percentage change from baseline in target lesion tumour size (Evaluable for response analysis set)	ZEFF_spider	For quarterly reviews, the figure is: Figure 11.2.1.7.1	X	X			
Figure 14.2.1.7.4	Spider plot showing the percentage change from baseline in target lesion tumour size (Evaluable for confirmed response analysis set)	ZEFF_spider	For futility and interim analyses only.					X
Figure 14.2.1.7.3	Spider plot showing the sum of diameters of target lesions (Evaluable for response analysis set)	ZEFF_spider	For quarterly reviews, the figure is: Figure 11.2.1.7.2	X	X			
Figure 14.2.1.7.5	Spider plot showing the sum of diameters of target lesions (Evaluable for confirmed response analysis set)	ZEFF_spider	For interim analyses only.					X
Table 14.2.1.8.1	Best percentage change from baseline in target lesion size (Evaluable for response analysis set)	TEFF190		X				
Figure 14.2.1.8.2	Waterfall plot of best percentage change from baseline in tumour size (Evaluable for response analysis set)	ZEFF030	For quarterly reviews, the figure is: Figure 11.2.1.8	X	X			

Figure 14.2.1.8.3	Waterfall plot of best percentage change from baseline in tumour size (Evaluable for confirmed response analysis set)	ZEFF030	Requested for M11 futility analysis.					

New lesions

Efficacy – CCI	
Table 14.2.1.9.1	CCI [redacted]
Table 14.2.1.9.2	

Subsequent cancer therapy

Efficacy – CCI	
Table 14.2.1.10.1	CCI [redacted]
Table 14.2.1.10.2	
Table 14.2.1.10.3	

14.2.2 Immunogenicity/Pharmacokinetics

Immunogenicity

Table 14.2.2.1	Summary of anti-drug antibodies (Safety analysis set)	SPADA1	Not applicable for Modules 8 and 11	X				
PK								
Table 14.2.2.2.1	Actual dose (mg) of durvalumab for each cohort (PK analysis set)	PK1	Apply only for Modules 6 and 10	X				
Table 14.2.2.2.2	Actual dose (mg/kg) of AZDXXXX for each cohort (PK analysis set)	PK1	Apply only for Modules 6 and 10	X				
Table 14.2.2.3.1	Summary of plasma concentrations (ng/mL) of durvalumab for each cohort (PK analysis set)	PK3(i)	Apply only for Modules 6 and 10	X				
Table 14.2.2.3.2	Summary of plasma concentrations (ng/mL) of AZDXXXX for each cohort (PK analysis set)	PK3(i)	Apply only for Modules 6, 7 and 10	X				
Figure 14.2.2.3.3	Geometric mean (gSD) plasma trough concentration of durvalumab versus study daytime by cohort (Linear scale) (PK analysis set)	PK2 (iii)	Apply only for Modules 6 and 10	X				
Figure 14.2.2.3.4	Geometric mean (gSD) plasma trough concentration of AZDXXXX versus study daytime by cohort (Linear scale) (PK analysis set)	PK2 (iii)	Apply only for Modules 6 and 10	X				
Figure 14.2.2.3.5	Geometric mean (gSD) plasma post-dose concentration of durvalumab	PK2 (iii)	Apply only for Module 10	X				

	versus study daytime by cohort (Linear scale) (PK analysis set)							
Figure 14.2.2.3.6	Geometric mean (gSD) plasma post-dose concentration of AZDXXXX versus study daytime by cohort (Linear scale) (PK analysis set)	PK2 (iii)	Apply only for Module 10	X				

14.3.1 Extent of Exposure

Extent of Exposure								
Table 14.3.1.1	Duration of durvalumab exposure (Safety analysis set)	TEXP010	Not applicable for Modules 8 and 11. For quarterly reviews, the table is: Table 11.3.1.1	X	X			X
Table 14.3.1.2	Duration of AZDXXXX exposure (Safety analysis set)	TEXP010	Requested for M11 futility analysis. For quarterly reviews, the table is: Table 11.3.1.2	X	X			X
Table 14.3.1.3.1	Dose intensity of durvalumab (Safety analysis set)	TEXP100	Not applicable for Modules 8 and 11	X				X
Table 14.3.1.3.2	Dose intensity of AZDXXXX (Safety analysis set)	TEXP100		X				X
Table 14.3.1.4	Time to first dose delay/interruption (Safety analysis set)	TEXP010	For quarterly reviews, the table is: Table 11.3.1.3	X	X			X
Table 14.3.1.5.1	Treatment interruptions and delays of durvalumab (Safety analysis set)	TEXP040	Not applicable for Modules 8 and 11	X				X
Table 14.3.1.5.2	Treatment interruptions and dose reductions of AZDXXXX (Safety analysis set)	TEXP040	For the modules where AZDxx is IV drug, the title will be:	X				X

			Treatment interruptions, dose reductions and delays of AZDxxx					
Table 14.3.1.6	Treatment cycles received (Safety analysis set)	TEXP080	For quarterly reviews, the table is: Table 11.3.1.6	X				

STATISTICAL ANALYSIS PLAN

Sponsor:	AstraZeneca	Protocol/CIP Number:	D6185C00001/Multiple drugs
CIL Project Number:	40773		

Safety

Safety	Present each module on a separate page. - Module 1: Cohort A.1.HRR, Cohort A.1. LKB, Cohort B.1.PRI, Cohort B.1.ACQ - Module 2: Cohort B.2.PRI, Cohort B.2.ACQ - Module 3: Cohort A.3.ATM, Cohort B.3.PRI, Cohort B.3.ACQ - Module 4: Cohort A4.RIC - Module 5: Cohort A.5.73H, Cohort B.5.PRI, Cohort B.5.ACQ - Module 6: Cohort A.6.HER2e, Cohort A.6.HER2m - Module 7: Total - Module 8: Cohort A.8.ATM - Module 9: Cohort B.9.PRI, Cohort B.9.ACQ - Module 10: Cohort C.10.160 (PRI and ACQ), Cohort C.10.240 (PRI and ACQ) - Module 11: Cohort C.11.240.PRI, Cohort C.11.240.ACQ AZDXXXX should be populated with the study drug for that module (Olaparib, AZD9150, AZD6738, Vistusertib, Oleclumab, trastuzumab deruxtecan, Cediranib)

Distribution: *Original:* *Copy:*

14.3.2 All Adverse Events

All Adverse Events								
Table 14.3.2.1	Adverse Events in any category - subject level (Safety analysis set)	TAE010	Requested for M11 futility analysis. For quarterly reviews, the table is: Table 11.3.2.1	X	X			X
Table 14.3.2.2	Adverse events in any category - episode level (Safety analysis set)	TAE020		X				
Table 14.3.2.3.1	Adverse Events by system organ class and preferred term (Safety analysis set)	S9 (i)	Requested for M11 futility analysis. For quarterly reviews, the table is: Table 11.3.2.3.1	X	X			X
Table 14.3.2.3.2	Number of adverse events, by system organ class and preferred term (Safety analysis set)	S16 (i)		X				
Table 14.3.2.3.3	Adverse Events by system organ class and preferred term (Screen Failures)	S9 (i)		X			X	
Table 14.3.2.3.4	Number of adverse events, by system organ class and preferred term (Screen Failures)	S16 (i)		X			X	
Table 14.3.2.5.1	Adverse events by system organ class, preferred term and maximum reported CTCAE grade (Safety analysis set)	TAE050		X				

Table 14.3.2.6.1	Adverse Events of CTCAE grade 3 or higher by system organ class and preferred term (Safety analysis set)	TAE060	Requested for M11 futility analysis. For quarterly reviews, the table is: Table 11.3.2.13	X	X			X

Causally Related Adverse Events

Causally Related Adverse Events								
Table 14.3.2.4.1	Causally related, to any treatment, adverse events by system organ class and preferred term (Safety analysis set)	S9 (ii)	For quarterly reviews, the table is: Table 11.3.2.4 Not applicable for Modules 8 and 11	X	X			
Table 14.3.2.4.2	Causally related, to durvalumab only, adverse events by system organ class and preferred term (Safety analysis set)	S9 (ii)	For quarterly reviews, the table is: Table 11.3.2.5 Not applicable for Modules 8 and 11	X	X			
Table 14.3.2.4.3	Causally related, to AZDXXXX only, adverse events by system organ class and preferred term (Safety analysis set)	S9 (ii)	For quarterly reviews, the table is: Table 11.3.2.6	X	X			
Table 14.3.2.4.4	Causally related, to durvalumab and AZDXXX, adverse events by system organ	S9 (ii)	For quarterly reviews, the table is: Table 11.3.2.7	X	X			

	class and preferred term (Safety analysis set)		Not applicable for Modules 8 and 11					
Table 14.3.2.5.2	Causally related, to any treatment, adverse events by system organ class, preferred term and maximum reported CTCAE grade (Safety analysis set)	TAE050	Not applicable for Modules 8 and 11	X				
Table 14.3.2.5.3	Causally related, to durvalumab only, adverse events by system organ class, preferred term and maximum reported CTCAE grade (Safety analysis set)	TAE050	Not applicable for Modules 8 and 11	X				

Table 14.3.2.5.4	Causally related, to AZDXXXX only, adverse events by system organ class, preferred term and maximum reported CTCAE grade (Safety analysis set)	TAE050		X				
Table 14.3.2.5.5	Causally related, to durvalumab and AZDXXXX, adverse events by system organ class, preferred term and maximum reported CTCAE grade (Safety analysis set)	TAE050	Not applicable for Modules 8 and 11	X				
Table 14.3.2.6.2	Causally related, to any treatment, adverse events of CTCAE grade 3 or higher by system organ class and preferred term (Safety analysis set)	S9 (ii)	For quarterly reviews, the table is: Table 11.3.2.14 Not applicable for Modules 8 and 11	X	X			
Table 14.3.2.6.3	Causally related, to durvalumab only, adverse events of CTCAE grade 3 or higher	S9 (ii)	For quarterly reviews, the table is: Table 11.3.2.15	X	X			

	by system organ class and preferred term (Safety analysis set)		Not applicable for Modules 8 and 11					
Table 14.3.2.6.4	Causally related, to AZDXXXX only, adverse events of CTCAE grade 3 or higher by system organ class and preferred term (Safety analysis set)	S9 (ii)	For quarterly reviews, the table is: Table 11.3.2.16	X	X			
Table 14.3.2.6.5	Causally related, to durvalumab and AZDXXXX, adverse events of CTCAE grade 3 or higher by system organ class and preferred term (Safety analysis set)	S9 (ii)	For quarterly reviews, the table is: Table 11.3.2.17 Not applicable for Modules 8 and 11	X	X			

Adverse Events leading to dose interruption, dose reduction, dose delay

Adverse Events leading to dose interruption, dose reduction								
Table 14.3.2.7.1	Adverse events leading to dose interruption of durvalumab by system organ class and preferred term (Safety analysis set)	S22	For quarterly reviews, the table is: Table 11.3.5.3.1 Not applicable for Modules 8 and 11	X	X			
Table 14.3.2.7.2	Adverse events leading to dose interruption of AZDXXXX by system organ class and preferred term (Safety analysis set)	S22	For quarterly reviews, the table is: Table 11.3.5.3.2	X	X			

Table 14.3.2.7.3	Adverse events leading to dose reduction of AZDXXXX by system organ class and preferred term (Safety analysis set)	S22	For quarterly reviews, the table is: Table 11.3.5.3.3	X	X			
Table 14.3.2.7.4	Adverse events leading to dose delay of durvalumab, by system organ class and preferred term (Safety analysis set)	S22	For quarterly reviews, the table is: Table 11.3.5.3.4 Not applicable for Modules 8 and 11	X	X			
Table 14.3.2.7.5	Adverse events leading to dose delay of AZDXXXX, by system organ class and preferred term (Safety analysis set)	S22	For quarterly reviews, the table is: Table 11.3.5.3.5	X	X			

Dose limiting Toxicity

Dose limiting Toxicity								
Table 14.3.2.8	Dose Limiting Toxicity events (Safety analysis set)	TAE410	Apply only for Module 6	X				

14.3.3 Death

Deaths								
Table 14.3.3.1.1	All subject deaths (Safety analysis set)	TDTH010	Requested for M11 futility analysis. For quarterly	X	X			X

			reviews, the table is: Table 11.3.3.1.1					
Table 14.3.3.1.2	Adverse events with outcome of death, by system organ class and preferred term (Safety analysis set)	S13 (i)	For quarterly reviews, the table is: Table 11.3.3.1.2	X	X			X
Table 14.3.3.1.3	Causally related, to any treatment, adverse events with outcome of death by system organ class and preferred term (Safety analysis set)	S13 (i)	For quarterly reviews, the table is: Table 11.3.5.3.6 Not applicable for Modules 8 and 11	X	X			
Table 14.3.3.1.4	Causally related, to durvalumab only, adverse events with outcome of death by system organ class and preferred term (Safety analysis set)	S13 (i)	Not applicable for Modules 8 and 11	X				
Table 14.3.3.1.5	Causally related, to AZDXXXX only, adverse events with outcome of death by system organ class and preferred term (Safety analysis set)	S13 (i)		X				
Table 14.3.3.1.6	Causally related, to durvalumab and AZDXXXX, adverse events with outcome of death by system organ class and preferred term (Safety analysis set)	S13 (i)	Not applicable for Modules 8 and 11	X				
Table 14.3.3.2.1	Listing of deaths (ITT analysis set)	TDTH040	For quarterly reviews, the table is: Table 11.3.3.2.1	X		M6, M8, M9		

Table 14.3.3.2.2	Adverse events with outcome of death - key subject information (Safety analysis set)	S14		X		M6, M8, M9		
Table 14.3.4.1.12	Serious adverse events with outcome of death by system organ class and preferred term (Safety analysis set)	TAE180		X				
Table 14.3.4.1.13	Causally related, to any treatment, serious adverse events with outcome of death by system organ class and preferred term (Safety analysis set)	S17(ii)	Not applicable for Modules 8 and 11	X				
Table 14.3.4.1.14	Causally related, to durvalumab only, serious adverse events with outcome of death by system organ class and preferred term (Safety analysis set)	S17(ii)	Not applicable for Modules 8 and 11	X				
Table 14.3.4.1.15	Causally related, to AZDXXXX only, serious adverse events with outcome of death by system organ class and preferred term (Safety analysis set)	S17(ii)		X				
Table 14.3.4.1.16	Causally related, to durvalumab and AZDXXXX, serious adverse events with outcome of death by system organ class and preferred term (Safety analysis set)	S17(ii)	Not applicable for Modules 8 and 11	X				

14.3.4 Serious Adverse Events

Serious Adverse Events

Table 14.3.4.1.1.1	Serious adverse events by system organ class and preferred term (Safety analysis set)	S17(i)	Requested for M11 futility analysis.	X				
Table 14.3.4.1.1.2	Number of serious adverse events, by system organ class and preferred term (Safety analysis set)	S16(ii)		X				
Table FDAAA1	Non-serious adverse events occurring in greater than 5% of subjects (Safety analysis set)	FDAAA1	Only for compulsory regulatory reporting requirements (FDA: Food and Drug Administration regulations), not included for CSR					
Table 14.3.4.1.7	Serious adverse events by system organ class and preferred term and maximum reported CTCAE grade (Safety analysis set)	TAE050		X				
Table 14.3.4.2	Serious adverse events - Listing of key information for SAEs (Safety analysis set)	TAE180	For quarterly reviews, the table is: Table 11.3.4.1.1	X	X			X

Causally Related Serious Adverse Events

Causally Related Serious Adverse Events								
Table 14.3.4.1.3	Causally related, to any treatment, serious adverse events by system organ class and preferred term (Safety analysis set)	S17(ii)	Not applicable for Modules 8 and 11	X				
Table 14.3.4.1.4	Causally related, to durvalumab only, serious adverse events by system organ	S17(ii)	Not applicable for Modules 8 and 11	X				

	class and preferred term (Safety analysis set)							
Table 14.3.4.1.5	Causally related, to AZDXXXX only, serious adverse events by system organ class and preferred term (Safety analysis set)	S17(ii)		X				
Table 14.3.4.1.6	Causally related, to durvalumab and AZDXXXX, serious adverse events by system organ class and preferred term (Safety analysis set)	S17(ii)	Not applicable for Modules 8 and 11	X				
Table 14.3.4.1.8	Causally related, to any treatment, serious adverse events by system organ class and preferred term and maximum reported CTCAE grade (Safety analysis set)	TAE050	Not applicable for Modules 8 and 11	X				
Table 14.3.4.1.9	Causally related, to durvalumab only, serious adverse events by system organ class and preferred term and maximum reported CTCAE grade (Safety analysis set)	TAE050	Not applicable for Modules 8 and 11	X				
Table 14.3.4.1.10	Causally related, to AZDXXXX only, serious adverse events by system organ class and preferred term and maximum reported CTCAE grade (Safety analysis set)	TAE050		X				
Table 14.3.4.1.11	Causally related, to durvalumab and AZDXXXX, serious adverse events by	TAE050	Not applicable for Modules 8 and 11	X				

	system organ class and preferred term and maximum reported CTCAE grade (Safety analysis set)							

14.3.5 Adverse Events Leading to Discontinuation

Adverse Events Leading to Discontinuation								
Table 14.3.5.1.1	Adverse events leading to discontinuation of any treatment, by system organ class and preferred term (Safety analysis set)	S19 (i)	For quarterly reviews, the table is: Table 11.3.5.1.1 Not applicable for Modules 8 and 11	X	X			X
Table 14.3.5.1.2	Adverse events leading to discontinuation of durvalumab only, by system organ class and preferred term (Safety analysis set)	S19 (i)	For quarterly reviews, the table is: Table 11.3.5.1.2 Not applicable for Modules 8 and 11	X	X			
Table 14.3.5.1.3	Adverse events leading to discontinuation of AZDXXXX only, by system organ class and preferred term (Safety analysis set)	S19 (i)	For quarterly reviews, the table is: Table 11.3.5.1.3	X	X			
Table 14.3.5.1.4	Adverse events leading to discontinuation of durvalumab and AZDXXXX by system organ class and preferred term (Safety analysis set)	S19 (i)	For quarterly reviews, the table is: Table 11.3.5.1.4 Not applicable for Modules 8 and 11	X	X			

Table 14.3.5.2	Adverse events leading to discontinuation of study treatment - Listing of key subject information (Safety analysis set)	TAE210		X				

Causally Related Adverse Events Leading to Discontinuation

Causally Related Adverse Events Leading to Discontinuation								
Table 14.3.5.1.5	Causally related, to any treatment, adverse events leading to discontinuation of durvalumab only by system organ class and preferred term (Safety analysis set)	S19 (ii)	Not applicable for Modules 8 and 11	X				
Table 14.3.5.1.6	Causally related, to any treatment, adverse events leading to discontinuation of AZDXXXX only by system organ class and preferred term (Safety analysis set)	S19 (ii)	Not applicable for Modules 8 and 11	X				
Table 14.3.5.1.7	Causally related, to any treatment, adverse events leading to discontinuation of durvalumab and AZDXXXX by system organ class and preferred term (Safety analysis set)	S19 (ii)	Not applicable for Modules 8 and 11	X				

14.3.6 Adverse Events of Special Interest and Infusion Related Adverse Events

Sponsor:	AstraZeneca	Protocol/CIP Number:	D6185C00001/Multiple drugs
CIL Project Number:	40773		

Adverse Events of Special Interest								
Table 14.3.6.1.1	Adverse events of special interest for durvalumab, by CTCAE grade (Safety analysis set)	TAE100	Not applicable for Modules 8 and 11	X		M6 M9		
Table 14.3.6.1.2	Adverse events of special interest for AZDXXXX, by CTCAE grade (Safety analysis set)	TAE100		X		M6		
Table 14.3.6.1.3	Adverse events of special interest for durvalumab by preferred term (Safety analysis set)	AS9	For quarterly reviews, the table is: Table 11.3.5.3.8 Not applicable for modules 8 and 11	X	X			
Table 14.3.6.1.4	Adverse events of special interest for AZDXXXX by preferred term (Safety analysis set)	AS9	For quarterly reviews, the table is: Table 11.3.5.3.9	X	X			
Table 14.3.6.1.5	Adverse events of special interest for durvalumab - list of preferred terms (Safety analysis set)	AS9	Not applicable for Modules 8 and 11	X		M6, M9		
Table 14.3.6.1.6	Adverse events of special interest for AZDxxxx - list of preferred terms (Safety analysis set)	AS9		X		M6		
Table 14.3.6.1.7	Infusion Related Adverse events by system organ class and preferred term (Safety analysis set)	S19 (i)	For quarterly reviews, the table is: Table 11.3.5.3.7 Not applicable for Modules 8 and 11	X	X			

Table 14.3.6.2	Adverse events of special and possible interest and immune mediated adverse events for durvalumab in any category - subject level (Safety analysis set)	TAE### 1		X				
Table 14.3.6.3.x	<<Insert Category>> Adverse events of special and possible interest and immune mediated adverse events for durvalumab (Safety analysis set)	TAE### 2		X				
Table 14.3.6.4	Adverse events of special and possible interest and immune mediated adverse events for durvalumab by maximum CTCAE grade (Safety analysis set)	TAE### 2 by grade		X				
Table 14.3.6.5	Immune mediated adverse events for durvalumab by preferred term (Safety analysis set)	TAE### 3		X				
Table 14.3.6.6	Adverse events of special interest for durvalumab by preferred term and by maximum CTCAE grade (Safety analysis set)	TAE### 3 by grade		X				
Table 14.3.6.7	Adverse events of special and possible interest and immune mediated adverse events for durvalumab time to event (Safety analysis set)	TAE### 4		X				
Table 14.3.6.8	Duration of high dose steroid use (days) for adverse events of special or possible interest for durvalumab (Safety analysis set)	TAE### 5		X				

Table 14.3.6.9	Adverse events of special interest for durvalumab, by outcome (Safety analysis set)	AESI_only		X				
Table 14.3.6.10	Adverse events of special or possible interest for durvalumab, by group term and preferred term (Safety analysis set)	AESI_AEPI		X				
Table 14.3.6.11	Number of patients with adverse events of special or possible interest, by outcome (Safety analysis set)	AESI_AEPI by outcome		X				
Table 14.3.6.12	Adverse events of special or possible interest, by group term and preferred term (Safety analysis set)	AESI_AEPI_event_rate		X				
Table 14.3.6.13	Adverse events of special or possible interest by grouped term, preferred term and maximum reported CTCAE grade (Safety analysis set)	AESI_AEPI_by_CTCAE_Grade		X				

14.3.7 Clinical Laboratory Evaluation

Clinical Laboratory Evaluation								
Table 14.3.7.1.1.1	Haematology laboratory variables over time (Safety analysis set)	S25 (lab)		X	AR			X
Table 14.3.7.1.1.2	Clinical chemistry laboratory variables over time (Safety analysis set)	S25 (lab)		X	AR			X

Sponsor:	AstraZeneca	Protocol/CIP Number:	D6185C00001/Multiple drugs
CIL Project Number:	40773		

Table 14.3.7.1.1.3	Coagulation variables over time (Safety analysis set)	S25 (lab)		X				X
Table 14.3.7.1.1.4	Laboratory parameters: Ratios (post-baseline / baseline) over time (Safety analysis set)			X				
Figure 14.3.7.1.2.x	Haematology laboratory data, box plot of < parameter (unit) > absolute values (Safety analysis set)	S11 (lab)		X				
Figure 14.3.7.1.3.x	Haematology parameters, box plot of <parameter (unit)> change from baseline (Safety analysis set)	S11 (lab)		X				
Figure 14.3.7.1.4.x	Clinical chemistry parameters, box plot of <parameter (unit)> absolute values (Safety analysis set)	S11 (lab)		X				
Figure 14.3.7.1.5.x	Clinical chemistry parameters, box plot of <parameter (unit)> change from baseline (Safety analysis set)	S11 (lab)		X				
Figure 14.3.7.1.6.x	Coagulation parameters, box plot of <parameter (unit)> absolute values (Safety analysis set)	S11 (lab)		X				
Figure 14.3.7.1.7.x	Coagulation, box plot of <parameter (unit)> change from baseline (Safety analysis set)	S11 (lab)		X				
Table 14.3.7.1.8.1	Haematology CTCAE grade change from baseline to maximum value on treatment (Safety analysis set)	TLAB020b		X				

Sponsor:	AstraZeneca	Protocol/CIP Number:	D6185C00001/Multiple drugs
CIL Project Number:	40773		

Table 14.3.7.1.8.2	Clinical chemistry CTCAE grade change from baseline to maximum post baseline value on treatment (Safety analysis set)	TLAB020b		X				
Table 14.3.7.1.8.3	Coagulation CTCAE grade change from baseline to maximum post baseline grade on treatment (Safety analysis set)	TLAB020b		X				
Table 14.3.7.1.9	Clinical Chemistry, CTCAE grade change from baseline to maximum on treatment for electrolytes and glucose (Safety analysis set)	TLAB020a		X				
Table 14.3.7.1.10	Subjects with combined ALT or AST, and bilirubin, elevations – individual subject data (Safety analysis set)	S32		X				
Figure 14.3.7.1.11	ALT versus total bilirubin expressed as multiples of the upper limit of normal (Safety analysis set)	S9		X				
Figure 14.3.7.1.12	AST versus total bilirubin expressed as multiples of the upper limit of normal (Safety analysis set)	S9		X				
Figure 14.3.7.1.13	Liver biochemistry test results over time - subjects with elevated ALT or AST, and elevated total bilirubin, and in which the elevation in transaminases precede or coincide with (that is, on the same day as) the elevation in TBL (Safety analysis set)	S10		X				

14.3.8 Vital Signs and ECG

Vital Signs, ECG and Ophthalmology								
Table 14.3.8.1.1.1	Vital signs over time (Safety analysis set)	S25 (vital)		X				X
Table 14.3.8.1.1.2	Summary of hypertension based on home BP measurements during study (Safety analysis set)	NEW7	Apply only for Module 7	X				
Table 14.3.8.1.1.3	Summary of hypotension based on home BP measurements during study (Safety analysis set)	NEW8	Apply only for Module 7	X				
Table 14.3.8.1.1.4	SpO2 over time (Safety analysis set)	S25	Apply only for Module 6	X				
Figure 14.3.8.1.2.x	Vital signs parameters, box plot of <parameter (unit)> absolute values (Safety analysis set)	ZVIT010		X				
Figure 14.3.8.1.3.x	Vital signs parameters, box plot of <parameter (unit)> change from baseline (Safety analysis set)	ZVIT010		X				
Table 14.3.8.1.4	ECG variables over time (Safety analysis set)	S25 (ecg)		X				X
Figure 14.3.8.1.5.x	ECG parameters, box plot of <parameter (unit)> absolute values (Safety analysis set)	S11 (ecg)		X				
Figure 14.3.8.1.6.x	ECG parameters, box-plot of <parameter (unit)> change from baseline (Safety analysis set)	S11 (ecg)		X				

Table 14.3.8.1.7	QTcF intervals, at any observation on treatment (Safety analysis set)	S35		X				
Table 14.3.9.1.1	LVEF over time (Safety analysis set)	S25	Apply only for Modules 6 and 7	X				
Table 14.3.9.1.2	LVEF Shift from baseline (Safety analysis set)	NEW9	Apply only for Modules 6 and 7	X				
Table 14.3.10.1.1	Visual Acuity over time (Safety analysis set)	S25	Apply only for Module 6	X				
Table 14.3.10.1.2	Ophthalmology assessments: Shift from baseline in fundoscopy and slit lamp examination (Safety analysis set)	NEW10	Apply only for Module 6	X				
Table 14.3.11	Potential interstitial lung disease events by maximum CTCAE grade per ILD adjudication committee (Safety analysis set)	AZTD967 AE01	Apply only for Module 6	X				

TFL number	**Title**	**Standard**	**Additional Information**	**CSR**	**Every 3 month review**	**SRC ***	**Screen Failure**	**IA Modules 10 and 11**
If Standard mock shell reference is GlobalSpec, a shell for guidance can be found in AZ document GLOBAL SPECIFICATION FOR CLINICAL STUDY REPORT APPENDIX 12.2 (SUBJECT DATA LISTINGS) v2.2 * Prior to CSP v10.0								

16.1.6 Batches of investigational products

Batches of investigational products								
Appendix 16.1.6.1	Subjects receiving the various batches of investigational products (Safety analysis set)	GlobalSpec		X				
Appendix 16.1.6.2	Subjects receiving the various batches of investigational products (Safety analysis set, Re-allocated to Module X)	GlobalSpec		X				

16.2.1 Subject Disposition

Patient Disposition								
Appendix 16.2.1.1	Subject disposition (Enrolled subjects)	GlobalSpec		X		M6 M8 M9		
Appendix 16.2.1.2	Subjects affected by the COVID-19 pandemic (ITT analysis set)	APL-COVID1		X				
Appendix 16.2.1.3	Subjects with reported issues in the Clinical Trial Management System due to COVID-19 pandemic (ITT analysis set)	APL-COVID2		X				
Appendix 16.2.1.4	Subject disposition (Screen Failures)	GlobalSpec					X	

Appendix 16.2.1.5	Subject disposition (Enrolled subjects, Re-allocated to Module X)	GlobalSpec		X				
Appendix 16.2.1.6	Subjects affected by the COVID-19 pandemic (ITT analysis set, Re-allocated to Module X)	APL-COVID1		X				
Appendix 16.2.1.7	Subjects with reported issues in the Clinical Trial Management System due to COVID-19 pandemic (ITT analysis set, Re-allocated to Module X)	APL-COVID2		X				
Appendix 16.2.1.8	Cohort allocation and stratification factors (Enrolled subjects)	GlobalSpec	Apply only for Modules 1, 3, 5, 6 and 8	X				
Appendix 16.2.1.9	Cohort allocation and stratification factors (Enrolled subjects, Re-allocated to Module X)	GlobalSpec	Apply only for Modules 1, 3, 5	X				

16.2.2 Protocol deviations

Protocol deviations								
Appendix 16.2.2.1	Subjects with important protocol deviations (ITT analysis set)	GlobalSpec	For quarterly review, the listings are: Appendix 12.2.2.1	X	X			
Appendix 16.2.2.2	Subjects with important protocol deviations (ITT analysis set, Re-allocated to Module X)	GlobalSpec		X	X			

16.2.3 Patients/data excluded from efficacy analysis

Patients/data excluded from efficacy analysis								
Appendix 16.2.3	Subjects excluded from the ITT analysis set (Enrolled subjects)	GlobalSpec		X				

16.2.4 Demographics and baseline characteristics

Demographics and baseline characteristics								
Appendix 16.2.4.1.1	Demographics and baseline characteristics, treated subjects (ITT analysis set)	GlobalSpec		X		M6, M8 M9		X
Appendix 16.2.4.1.2	Demographics and baseline characteristics (Screen Failures)	GlobalSpec		X			X	
Appendix 16.2.4.2.1	Prior anti-cancer therapy (ITT analysis set)	NEW11		X		M6, M8 M9		X
Appendix 16.2.4.2.2	Prior anti-cancer therapy (Screen Failures)	NEW12		X			X	
Appendix 16.2.4.2.3	Prior radiotherapy (ITT analysis set)	NEW13		X		M6, M8 M9		
Appendix 16.2.4.2.4	Prior radiotherapy (Screen Failures)	NEW14		X			X	
Appendix 16.2.4.2.5	Medical and surgical History (ITT analysis set)	NEW15		X		M6, M8 M9		
Appendix 16.2.4.2.6	Extent of Disease (ITT analysis set)	NEW16		X		M6, M8 M9		X
Appendix 16.2.4.2.7	Extent of Disease (Screen Failures)	NEW17		X			X	

Sponsor:	AstraZeneca	Protocol/CIP Number:	D6185C00001/Multiple drugs
CIL Project Number:	40773		

Appendix 16.2.4.2.8	Pathology of non-small cell lung cancer (ITT analysis set)	NEW18		X		M6, M8 M9		
Appendix 16.2.4.2.9	Pathology of non-small cell lung cancer (Screen Failures)	NEW19		X			X	
Appendix 16.2.4.2.10	Disease characteristics at baseline (ITT analysis set)	NEW20		X		M6, M8 M9		X
Appendix 16.2.4.2.11	Disease characteristics at baseline (Screen Failures)	NEW21		X			X	
Appendix 16.2.4.2.12	Concomitant Procedures (ITT analysis set)	NEW22		X				
Appendix 16.2.4.2.13	Concomitant medications on entry and during the study (ITT analysis set)	GlobalSpec		X		M6, M8 M9		
Appendix 16.2.4.2.14	Substance use (ITT analysis set)	NEW23		X				
Appendix 16.2.4.2.15	CCI							
Appendix 16.2.4.2.16								
Appendix 16.2.4.2.17								
Appendix 16.2.4.3.1	Demographics and baseline characteristics, treated subjects (ITT analysis set, Re-allocated to Module X)	GlobalSpec		X				

Sponsor:	AstraZeneca	Protocol/CIP Number:	D6185C00001/Multiple drugs
CIL Project Number:	40773		

Appendix 16.2.4.4.1	Prior anti-cancer therapy (ITT analysis set, Re-allocated to Module X)	NEW11		X				
Appendix 16.2.4.4.3	Prior radiotherapy (ITT analysis set, Re-allocated to Module X)	NEW13		X				
Appendix 16.2.4.4.5	Medical and surgical History (ITT analysis set, Re-allocated to Module X)	NEW15		X				
Appendix 16.2.4.4.6	Extent of Disease (ITT analysis set, Re-allocated to Module X)	NEW16		X				
Appendix 16.2.4.4.8	Pathology of non-small cell lung cancer (ITT analysis set, Re-allocated to Module X)	NEW18		X				
Appendix 16.2.4.4.10	Disease characteristics at baseline (ITT analysis set, Re-allocated to Module X)	NEW20		X				
Appendix 16.2.4.4.12	Concomitant Procedures (ITT analysis set, Re-allocated to Module X)	NEW22		X				
Appendix 16.2.4.4.13	Concomitant medications on entry and during the study (ITT analysis set, Re-allocated to Module X)	GlobalSpec		X				
Appendix 16.2.4.4.14	Substance use (ITT analysis set, Re-allocated to Module X)	NEW23		X				

Appendix 16.2.4.4.15	CCI [redacted]							
Appendix 16.2.4.4.17	Subsequent radiotherapy (ITT analysis set, Re-allocated to Module X)	NEW26		X				

16.2.5 Treatment compliance and drug concentration data

Exposure								
Appendix 16.2.5.1.1	Treatment administration and dose modifications of IV drug (Safety analysis set)	APL09	Not applicable for Modules 8 and 11	X		M6, M9		X
Appendix 16.2.5.1.2	Treatment administration and dose modifications of oral drug (Safety analysis set)	APL09	Apply only for Modules 1, 3, 7, 8, 9, 10 and 11	X		M6, M8 M9		
Appendix 16.2.5.2	Duration of exposure and dose intensity (Safety analysis set)	NEW27		X		M6, M8 M9		
Appendix 16.2.5.3	Overdose Report (Safety analysis set)	NEW28		X		M6, M8 M9		
Appendix 16.2.5.4.1	Treatment administration and dose modifications of IV drug (Safety analysis set, Re-allocated to Module X)	APL09		X				
Appendix 16.2.5.4.2	Treatment administration and dose modifications of oral drug (Safety	APL09		X				

	analysis set, Re-allocated to Module X)							
Appendix 16.2.5.5	Duration of exposure and dose intensity (Safety analysis set, Re-allocated to Module X)	NEW27		X				
Appendix 16.2.5.6	Overdose Report (Safety analysis set, Re-allocated to Module X)	NEW28		X				

16.2.6 Efficacy, PK and Biomarker response data

Efficacy, PK and Biomarker response data								
Appendix 16.2.6.1.1	Tumour assessment details for subject Exxxxxxx (RECIST 1.1) (ITT analysis set)	EFF011(A), EFF011 (B), EFF011 (C), EFF011 (D), EFF011 (E), EFF011 (F)	For quarterly review, the listings are: Appendix 12.2.6.1.1	X	X			XX
Appendix 16.2.6.1.2	Best objective response, duration of response (Evaluable for response analysis set)	NEW29		X				
Appendix 16.2.6.1.3	Disease control at 12 weeks and 24 weeks (Evaluable for response analysis set)	NEW30		X				
Appendix 16.2.6.1.4	Progression details (ITT analysis set)	NEW31		X				
Appendix 16.2.6.1.5	Overall survival (ITT analysis set)	NEW32		X				

Appendix 16.2.6.1.6	Overall survival (Screen Failures)	NEW33		X			X	
Appendix 16.2.6.1.7	Survival Status (ITT analysis set)	NEW34		X				
Appendix 16.2.6.2.1	Individual plasma concentration (PK analysis set)	NEW35		X				
Appendix 16.2.6.2.2	Anti-drug antibody results (Safety analysis set)	SPADA1	Not applicable for Modules 8 and 11	X				
Appendix 16.2.6.3.1	Tumour Biomarker Profile (ITT analysis set)	NEW36		X				
Appendix 16.2.6.3.2	Tumour Biomarker Profile (Screen Failures)	NEW37		X			X	

16.2.7 Adverse events

Adverse events								
Appendix 16.2.7.1	Adverse events (Safety analysis set)	GlobalSpec		X		M6, M8 M9		X
Appendix 12.2.7.1.1	Adverse events of CTCAE Grade 4 only (Safety Analysis Set)	GlobalSpec	For quarterly reviews only		AR			
Appendix 16.2.7.2	Adverse events (Screen Failures)	GlobalSpec		X			X	
Appendix 16.2.7.3	Adverse events occurring prior to the first dose of any study drug (Safety analysis set)	GlobalSpec		X		M6, M8 M9		

Appendix 16.2.7.4	Serious adverse events (Screen Failures)	GlobalSpec		X			X	
Appendix 16.2.7.5	Procedure related adverse events including 21 days after tumour biopsy procedure (Safety analysis set)	GlobalSpec		X				
Appendix 16.2.7.6	Adverse events occurring after the 90-day follow-up period (Safety analysis set)	GlobalSpec		X		M6, M8 M9		
Appendix 16.2.7.7	Dose Limiting Toxicity events (Safety analysis set)	NEW38	Apply only for Module 6	X		M6		
Appendix 16.2.7.8	Serious adverse events (Safety analysis set)	GlobalSpec		X				
Appendix 16.2.7.9	Adverse events for subjects with confirmed/suspected COVID-19 infection (Safety analysis set)	GlobalSpec		X				
Appendix 16.2.7.10	Adverse events (Safety analysis set, Re-allocated to Module X)	GlobalSpec		X				
Appendix 16.2.7.11	Adverse events occurring prior to the first dose of any study drug (Safety analysis set, Re-allocated to Module X)	GlobalSpec		X				
Appendix 16.2.7.12	Adverse events occurring after the 90-day follow-up period (Safety analysis set, Re-allocated to Module X)	GlobalSpec		X				

Appendix 16.2.7.13	Serious adverse events (Safety analysis set, Re-allocated to Module X)	GlobalSpec		X				
Appendix 16.2.7.14	Adverse events for subjects with confirmed/suspected COVID-19 infection (Safety analysis set, Re-allocated to Module X)	GlobalSpec		X				
Appendix 16.2.7.15	Listing of adverse events of special and possible interest for durvalumab (Safety analysis set)	LAESI01		X				
Appendix 16.2.7.16	Listing of time to and duration of systemic steroids for immune-mediated adverse events for durvalumab (Safety analysis set)	LAESI02		X				
Appendix 16.2.7.17	Listing of time to Onset/Resolution of Immune Mediated Adverse Events for durvalumab (Safety analysis set)	LAESI03		X				
Appendix 16.2.7.18	Other adverse events of special interest: ILD/pneumonitis (Safety analysis set)	APL14_2ILD	Apply only for Module 6	X				
Appendix 16.2.7.19	Interstitial lung disease examination (Safety analysis set)	APLILD1	Apply only for Module 6	X				

16.2.8 Laboratory assessments

Sponsor:	AstraZeneca	Protocol/CIP Number:	D6185C00001/Multiple drugs
CIL Project Number:	40773		

Laboratory assessments								
Appendix 12.2.4.1	Results of COVID-19 Tests at the local Laboratory	NEW	For quarterly reviews only					
Appendix 16.2.8.1	Individual laboratory results - Haematology (Safety analysis set)	GlobalSpec		X		M6, M8 M9		
Appendix 16.2.8.2	Individual laboratory results - Clinical chemistry (Safety analysis set)	GlobalSpec		X		M6, M8 M9		
Appendix 16.2.8.3	Individual laboratory results - Coagulation (Safety analysis set)	GlobalSpec		X		M6, M8 M9		
Appendix 16.2.8.4	Individual laboratory results - Urinalysis (Safety analysis set)	GlobalSpec		X		M6, M8 M9		
Appendix 16.2.8.5	Positive Pregnancy Results (Safety analysis set)	GlobalSpec		X		M6, M8 M9		
Appendix 16.2.8.6	Liver assessment for all potential Hy's Law cases (Safety analysis set)	GlobalSpec		X		M6, M8 M9		
Appendix 16.2.8.7	Liver risk factors for all potential Hy's Law cases (Safety analysis set)	GlobalSpec		X		M6, M8 M9		
Appendix 16.2.8.8	Liver signs and symptoms for all potential Hy's Law cases (Safety analysis set)	GlobalSpec		X		M6, M8 M9		
Appendix 16.2.8.9	Individual laboratory results - Haematology (Safety analysis set, Re-allocated to Module X)	GlobalSpec		X				

Appendix 16.2.8.10	Individual laboratory results - Clinical chemistry (Safety analysis set, Re-allocated to Module X)	GlobalSpec		X				
Appendix 16.2.8.11	Individual laboratory results - Coagulation (Safety analysis set, Re-allocated to Module X)	GlobalSpec		X				
Appendix 16.2.8.12	Individual laboratory results - Urinalysis (Safety analysis set, Re-allocated to Module X)	GlobalSpec		X				
Appendix 16.2.8.13	Positive Pregnancy Results (Safety analysis set, Re-allocated to Module X)	GlobalSpec		X				
Appendix 16.2.8.14	Liver assessment for all potential Hy's Law cases (Safety analysis set, Re-allocated to Module X)	GlobalSpec		X				
Appendix 16.2.8.15	Liver risk factors for all potential Hy's Law cases (Safety analysis set, Re-allocated to Module X)	GlobalSpec		X				
Appendix 16.2.8.16	Liver signs and symptoms for all potential Hy's Law cases (Safety analysis set, Re-allocated to Module X)	GlobalSpec		X				

16.2.9 Other safety data

Other safety data

Sponsor:	AstraZeneca	Protocol/CIP Number:	D6185C00001/Multiple drugs
CIL Project Number:	40773		

Appendix 16.2.9.1	Vital Signs (Safety analysis set)	GlobalSpec		X		M6, M8 M9		X
Appendix 16.2.9.2	Additional BP measurements by subjects at home (Safety analysis set)	NEW39	Apply only for Module 7	X				
Appendix 16.2.9.3	Pulmonary function test and Pulmonary HRCT/MRI (Safety analysis set)	NEW40	Apply only for Module 6	X		M6		
Appendix 16.2.9.4	Oxygen Saturation (Safety analysis set)	NEW41	Apply only for Module 6	X		M6		
Appendix 16.2.9.5	Vital Signs (Safety analysis set, Re-allocated to Module X)	GlobalSpec		X				
Appendix 16.2.10.1	ECG data (Safety analysis set)	GlobalSpec		X		M6		X
Appendix 16.2.10.2	ECG Findings (Safety analysis set)	GlobalSpec		X		M6		X
Appendix 16.2.10.3	Ejection Fraction Measurements - MUGA / ECHO scan (Safety analysis set)	NEW42	Apply only for Modules 6 and 7	X		M6		
Appendix 16.2.10.4	Visual assessments (Safety analysis set)	NEW43	Apply only for Module 6	X		M6		
Appendix 16.2.10.5	Physical examination findings (Safety analysis set)	GlobalSpec		X				

Appendix 16.2.10.6	ECOG status (Safety analysis set)	NEW44		X				
Appendix 16.2.10.7	ECG data (Safety analysis set, Re-allocated to Module X)	GlobalSpec		X				
Appendix 16.2.10.8	ECG Findings (Safety analysis set, Re-allocated to Module X)	GlobalSpec		X				
Appendix 16.2.10.9	Physical examination findings (Safety analysis set, Re-allocated to Module X)	GlobalSpec		X				
Appendix 16.2.10.10	ECOG status (Safety analysis set, Re-allocated to Module X)	NEW44		X				