- **Protocol number: D419QC00002**
- **Document title: A Phase II, Open-Label, Multi-Arm Study to Determine the Preliminary Efficacy of Novel Combinations of Treatment in Patients with Platinum Refractory Extensive-Stage Small-Cell Lung Cancer (BALTIC)**
- **NCT number: NCT02937818**
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- **Date of the document: 16 January 2020**

Clinical Study Protocol

Drug Substance	Durvalumab (MEDI4736), tremelimumab, AZD1775, carboplatin, olaparib, ceralasertib (AZD6738)
Study Code	D419QC00002
Version	05
Date	16Jan2020
EudraCT Number	2016-001202-42

A Phase II, Open-Label, Multi-Arm Study to Determine the Preliminary Efficacy of Novel Combinations of Treatment in Patients with Platinum Refractory Extensive-Stage Small-Cell Lung Cancer (BALTIC)

Sponsor:

AstraZeneca AB, 151 85 Södertälje, Sweden

The following Amendment(s) and Administrative Changes have been made to this protocol since the date of preparation:

Amendment No.	Date of Amendment	Local Amendment No:	Date of Local Amendment
1	01Jul2016		
2	30 Mar2017		
3	15Dec 2017		
4	25June 2018		
5	16Jan2020		

Administrative Change No.	Date of Administrative Change	Local Administrative Change No.	Date of Local Administrative Change

VERSION HISTORY

Version 05, 16Jan2020
The following changes were incorporated into version 05 of the protocol: • Sections on durvalumab and tremelimumab monotherapies and combined therapy updated as per current IBs in Appendix A. **Sections updated: 2.7.2.1, 2.7.2.2, 2.7.2.3 and 7.6** • Dosing Modification and Toxicity Management Guidelines for durvalumab and tremelimumab separated from Appendix A (i.e. Arm A study protocol). Sections updated: **6.2.3, 7.5**, **(Section 7.5.2 added), and Appendix A1** (removed from Appendix A) • Removal of the requirement to collect PK samples after Cycle 6 in Arm C. **Sections updated: Appendix C Table 3 (schedule of assessments) and Section 7.2** • Haematological parameters for ongoing treatment, and guidance for dose modifications revised as per updated Cerelasertib guidance. **Sections updated: Appendix C, Section 8.4 (Dose modification and management of investigational product toxicities)** • Photosensitivity added to restrictions in Appendix C. **Section updated: Appendix C, Section 5.5.4** • Study drug name AZD6738 supplemented or replaced with ceralasertib across the protocol.

Version 04 , 25June 2018
The following changes were incorporated into version 04 of the protocol: • Protocol synopsis and Section 2.2.1 Rationale for study design were updated to allow expansion of any arm, to a total of 40 eligible subjects, based on Review Committee assessment of data from the first 20 subjects. • CCI [redacted]

- Synopsis Statistical Methods section and Section 9.2 Sample Size Estimate of Master protocol updated to correct typos, include a row in the table for 40 subjects and remove the column for CCI .
- Rationale for study design updated in Section 2.2.1 to clarify that the decision-making for moving to Stage II and expansion of arms will be a Review Committee assessment of the first 20 subjects, based on the totality of the data considering benefit-risk assesment.
- Figure 1 study design diagram updated to include Arm A expansion.
- Section 2.3 benefit-risk updated with 6 and 12 months OS data.
- Figure 2 of study design updated to include Arm A expansion.
- Information updated on exploratory objectives in Section 3.4 for consistency with synopsis.
- Inclusion criteria from Section 4.1 and exclusion criteria from Section 4.2 were deleted and added to criteria section in each arm appendix.
- Section 4.5 Methods for assigning treatment groups updated to clarify that parallel recruitment is allowed.
- Information added to Section 6.1 to clarify how to follow up if patients discontinue study treatment prior to PD.
- Section 6.2.1 Laboratory safety assessments has been updated to remove lists of variables measured as these are fully described in the individual arms.
- Section 6.2.5 Other safety assessments has been moved to Appendix for Arm A.
- CCI [redacted]
- Section 7.9 Study governance and oversight updated to clarify the role of Review Committee in decision-making
- Section 9.3.2 evaluable set definition has been deleted, including a sentence about replacing subjects (information on replacement has now been mentioned earlier in CSP).
- Wording describing expansion added to Section 9.5 Methods for statistical analyses.

- Section 9.5.8 Analysis following expansion added to explain there is no need for further interim analysis in that group of patients and describe planned sensitivity analysis.
- Section 10.3 Study timetable and end of study updated to be consistent with predicted end of trial as described in clinicaltrials.gov
- Wording was updated through protocol to streamline document, provide clarifications and make more user-friendly (e.g. clarified "study treatment commencement" instead of "study start"; provided references to appropriate appendix; corrected typos; renumbered tables etc)
- Appendix A Section 2.5 Rationale for study design, doses, and control groups updated to include scientific rationale for expanding Arm A.
- Appendix A Section 2.6 Durvalumab and tremelimumab dose and treatment regimen justification updated with latest data and durvalumab IB.
- Appendix A Figure 1 updated to reflect addition of Expansion patients
- Appendix A Section 4.1 and Section 4.2 updated to contain a complete set of inclusion and exclusion criteria. Mandatory provision of archival or fresh tumour sample added as an eligibility criterion for Arm A.
- Appendix A Table 2 Schedule of assessments updated to remove biomarker samples that are not collected (e.g. CCI), added (e.g. CCI) and tighten requirements for tumour biopsy material. Footnotes updated to clarify that some samples are not required in the expansion group (including PK, anti-drug antibodies (ADA) and mRNA).
- Appendix A Table 3 Schedule of assessments (post-discontinuation) updated regarding PK samples to clarify not required for expansion group.
- Appendix A Section 6 Study assesments updated to include laboratory variables and other safety assessments instead of these being in master protocol, and vital signs moved to Section 6.2 safety assessments.
- Appendix A section 6.3 CCI [redacted].
- Appendix B Section 3.4 updated to remove CCI as not relevant at this time.
- Appendix B Section 4.1 and Section 4.2 updated to contain a complete set of inclusion and exclusion criteria.

- Updates added to Appendix B Table 1 to reflect updates of protocol structure and to to remove need to collect CCI Footnote added to highlight the need to check haematology results prior to each cycle.
- Addition of footnote e in Appendix B Table 1 regarding availability of haematology results prior to dosing of each cycle.
- Appendix B section 6.1 Safety Assessments updated with the complete set of laboratory variables, moved from master protocol.
- Appendix B Section 7.3.1 updated with clarification to the dose modification guidance for haematological events with current safety guidance regarding AZD1775 plus carboplatin.
- Addition of Hepatitis B, C and HIV testing into Appendix C Table 3 Schedule of assessment for olaparib + AZD6738 combination therapy. RECIST schedule corrected to include the 12 week scan. Footnotes amended to remove redundant nausea and vomiting eCRF.
- Appendix C Section 7.4.5 and Table 3 updated to reflect the wording on optional exploratory genetic sample informed consent form, consistent with current durvalumab template.
- Appendix C Section 9.7.2 updated to reflect information included in latest olaparib IB (edition 15).
- Appendix F (RECIST) Section 4.1 Schedule of evaluation: wording amended from "confirmatory scan" to "follow up scan" and deleted sentence describing continuation of study drug past progression until confirmation, as it only applies to Arm A, which is fully described in Section 5 of this appendix.
- CCI
- List of References moved to Appendix K

Version 03, 15 December 2017

The following changes were incorporated into version 3.0 of the protocol:

- Treatment Arm C added to protocol – subprotocol for this Arm is included in APPENDIX C
- Appropriate section, figures and tables of this protocol updated to reflect addition of Arm C
- Changes related to the numbering of Sections and naming of Appendices updated to indicate the separation of treatment Arms
- Table of content updated to reflect changes in numbering and naming of Appendices throughout the protocol
- Minor editorial changes of a typographical nature made throughout the protocol for consistency and clarity. Several references to sections were updated for consistency across the protocol.
- Clarification to interim analysis description was added in Synopsis section to clarify the action taken in event of a decision to close Arm after stage 1
- List of References updated to reflect all added references. All references moved to Appendix J
- Exploratory objective and specification for Arms was added to Section 3.4, Study Objectives
- Information to refer to Arm specific criteria added to Section 4.1. and 4.2
- Clarification added to Section 4.9 on discontinuation of investigational product
- Information added in Section 4.10.2 regarding possible replacement of withdrawn patients
- Clarification was added in Section 4.10.3 on consent withdrawal
- Addition of Section 6.2.5 regarding Other Safety Assessments
- Information in Section 6.6.1.3 added on collection and processing of CCI samples
- Section 7.3.1, Time period for collection of adverse events, revised to address events post the defined safety follow-up period

- Section 7.3.2, Follow-up of unresolved adverse events, revised to align with current IB
- Information updated in Section 7.9 on study governance and oversight
- Information on Safety Analysis Set updated in table 9.3 and section 9.3.2
- Information added in section 9.3.1 to provide definition of evaluable patients
- Section 9.5.1 added to provide more clarity on clarity on Primary Analysis including OS analysis
- Clarification on patients included in safety and efficacy analyses added to Section 9.5.7
- Addition of timelines for publishing of safety and efficacy analyses added to Section 9.5.7
- Information updated in section 10.4 on data management
- Information updated in Section 11.3 on ethics and regulatory review
- Appendix A, Sections 2.2, 2.3, 2.4, 2.6.4, 2.6.5.1, 2.7.2, 4.6, 7.5, 7.6 and 8.1 content updated to align with current IBs
- Information added to Appendix A, Section 2.8 to provide clarity on study design for Arm A
- Additional clarification added to inclusion criteria regarding fulfilment of criteria in Appendix A, Section 4.1.
- Clarification added to inclusion criterion 5 in Appendix A, section 4.1 on prohibition of use of granulocyte-colony stimulating factor for neutrophils raising during screening
- Information regarding sample collection for biomarker analysis in Appendix A, section 6.2. added
- Clarification on sample disposition and timing of pharmacokinetic/ADA samples added to Appendix A, section 6.5
- Appendix A, Section 8.1.2 updated to clarify product storage
- Information updated in Appendix A, section 8.2.1 regarding re-consenting of patients

- Updated Appendix A Table 7 Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions (MEDI4736 Monotherapy or Combination therapy with Tremelimumab or Tremelimumab Monotherapy) to version from 1 Nov 2017
- Information added to Appendix B Section 2.6 to provide clarity on study design for Arm B
- Additional information added regarding exclusion criterion 8 in Appendix B section 4.2
- Additional information regarding sample collection for biomarker analysis added in Appendix B section 6.4
- Information was added to Appendix B Section 7.2.2 regarding paternal exposure
- Appendix B Section 7.3 updated to reflect latest PSSR
- Content moved from Appendix B2 to Appendix A Table 7 as the is common to all treatment arms. Duplicative parts related only to Arm B removed as already described in Appendix B section 8.7.1
- Additional information added in Appendix G regarding acceptable contraceptive methods

Version 02, 30 March 2017

- The following changes were incorporated into version 2.0 of the protocol:Minor editorial changes of a typographical nature were made throughout the protocol for consistency and clarity. Several references to sections were updated for accuracy.
- Changes related to the numeration were made for the majority of sections for consistency with the current protocol templates for durvalumab and AZD1775.
- Minor clarifications were made throughout the protocol for consistency with the current protocol templates for durvalumab and AZD1775.
- Clarification added regarding the number of patients to be enrolled in Synopsis, Section 1 and Section 2.4.
- Addition of the timelines between progression and enrolment to target population in Synopsis

- Changes related to weigh based dosing for patients whose weight falls to 30kg or below in Synopsis, Sections 2.6.1, 2.6.4, 2.6.6, 2.8, 8.1.1, 8.2.
- Minor clarification added to inclusion criteria 3 regarding stage at initial diagnosis.
- Clarification added to inclusion criteria 4 regarding the timelines between progression and enrolment
- Information added to Section 5 Study plan and timing of procedures regarding relevant assessments.
- Change related to the time of validity of laboratory samples between screening and baseline was from 7 days to 3 days in Section 6.2.1.
- Addition of Partial thromboplastin time into Table 2 “Hematology variables to be measured”.
- Information added to Section 6.2.3. Resting 12-lead ECGs regarding additional ECG monitoring for Arm B
- Minor clarification added to Section 7.6 Overdose
- Information added regarding sensitivity analysis in Section 9.5
- Information updated on number of patients who received durvalumab in Section 2.2, 2.4
- Additional information added on Study D4190C00006 Section 2.6.3.1
- Additional information added on Rationale for four cycles of combination therapy followed by durvalumab monotherapy Section 2.6.4.
- Removal of Section 12.7.1.2 Tremelimumab as there will be no tremelimumab monotherapy in the trial.
- Information added to Sections 2.7.2, 2.7.2.1, 2.7.2.2 and 2.7.2.3 regarding identified and potential risks for durvalumab, tremelimumab and durvalumab + tremelimumab.
- Information on blood donation was added to Section 4.6.
- Additional information added on intravaginal devices for contraception to Appendix A Table 1.
- Information added to Section 5 regarding reasons for potential dosing delay.

- Information added on Coagulation (PT/INR/PTT) requirements to Appendix A Table 2.
- Addition of footnote q that specifies the time of sample collection to Appendix A Table 2.
- Removal of footnote j from Appendix A Table 3 as this is for post discontinuation PK.
- Information added to Section 6.1 regarding ORR and confirmation of progression.
- Information added to Section 7.5 regarding Dosing Modification and Toxicity Management Guidelines for patients with new or worsening pulmonary symptoms.
- Information added to Section 7.5.1 regarding etiologic causes of the imAE.
- Additional clarification and information added to Section 7.6 regarding AESIs.
- Additional information added to Section 8.1.1 regarding durvalumab administration.
- Additional information added to Section 8.1.2 tremelimumab administration.
- Information added to Section 8.2.1 regarding progression during treatment.
- Information added to Appendix A Table 7 regarding Herbal and natural remedies as prohibited medication.
- Amendment of Appendix A1 Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions (MEDI4736 Monotherapy or Combination therapy with Tremelimumab or Tremelimumab Monotherapy) to version from 19 Aug 2016.
- Amendment of Section 2.5.2.1 regarding identified and potential risks for AZD1775.
- Clarification added to Section 4.1, inclusion criteria 4 regarding Cockcroft-Gault method GFR calculation.
- Clarification added to Section 4.2, exclusion criteria 10, and Section 8.7.1 regarding use of sensitive substrates of CYP3A4.
- Section 4.2, exclusion criteria 15 was moved under exclusion criteria 14.
- Addition of History of Torsades de pointes as exclusion criteria 15 to Section 4.2.
- Additional information added to Section 4.5 regarding AZD1775 dosing.

- Addition of a section regarding Patients with a history of Torsades de pointes to the Restrictions Section 4.5.2.
- Addition of ECG assessments on Cycle 1, Cycle 2 and Cycle 3 and beyond Appendix B Table 1. Adjustment of the text of footnote C in Appendix B Table 1 according to this change.
- Addition of Safety assessments and ECG to Section 6.
- Addition of Electrocardiogram QT corrected interval prolonged to Appendix B Table .
- Clarification added to section 7.3.3.3 Nausea and vomiting regarding aprepitant [Emend] and fosaprepitant.
- Addition of Section 7.3.3.6 QTc prolongation.
- Clarification added to Appendix B Figure 2 AZD1775 + carboplatin therapy dosing schedule.
- Addition of Section 8.7.3 Substances known to prolong the ECG QTc interval.
- Clarification added to Section Appendix B2 regarding the administration of AZD1775 with substances known to prolong the ECG QTc interval is not recommended and a list of medicines with a known risk of Torsades de pointes is provided.
- Additional information added to Appendix F Confirmation of progression.
- Appendix 3 Definition of Women of Childbearing Potential and Acceptable Contraceptive Methods was renamed to Appendix G
- Appendicies 1 for section A and 1 and 2 for section B were renamed to Appendix A Table 7, Appendix B1 New York Heart Association Criteria
- , and Appendix B2 respectively

Version 01, 01 July 2016
Initial creation

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

1. PROTOCOL SYNOPSIS

A Phase II, Open-Label, Multi-Arm Study to Determine the Preliminary Efficacy of Novel Combinations of Treatment in Patients with Platinum Refractory Extensive-Stage Small-Cell Lung Cancer

International Coordinating Investigator: Dr. med. Niels Reinmuth, Gauting, Germany

Study site(s) and number of patients planned

This study will enroll up to 40 eligible patients in each arm at approximately 30 sites using a 2-stage approach to recruitment, with the potential for expansion depending on data from the first 20 subjects. The study initially opened with 2 arms; additional treatment arms can be opened in a modular manner when a compelling rationale for the combination and a safe and tolerable dose has been provided. The total number of patients will depend on full enrolment of individual arms as well as the total number of treatment arms in the study.

Study period		Phase of development
Estimated date of first patient enrolled	Q3 2016	II
Estimated date of last patient completed	Q1 2021	II

Study design

This is a Phase II, open-label, multi-drug, multi-center, multi-arm, signal-searching study in patients with extensive-stage small-cell lung cancer (SCLC) who have refractory or resistant disease from prior platinum-based chemotherapy. This study will evaluate the preliminary efficacy, safety, tolerability, and immunogenicity of novel combinations of immunotherapies and/or deoxyribonucleic acid (DNA) damage repair inhibitors in patients with platinum refractory or resistant extensive stage-disease SCLC.

Patients who have progressive disease (PD) during first-line platinum-based chemotherapy (platinum refractory) or PD within 90 days after completing first-line platinum-based chemotherapy (platinum resistant) will be enrolled to the study.

The primary objective of the study is to assess the preliminary efficacy of each treatment arm based on objective response rate (ORR). Tumor assessment will be performed by Investigators either every 6 or 8 weeks ± 1 week depending on the treatment arm (relative to the date of initiation of study treatment) until confirmed objective disease progression (as defined by Response Evaluation Criteria in Solid Tumors, version 1.1 [RECIST 1.1]).

RECIST 1.1 measurements will be used to programmatically derive the primary variable of ORR and secondary variables of duration of response (DoR), disease control rate (DCR), time to response (TTR), and progression-free survival (PFS). ORR (complete response [CR] or

partial response [PR]) should be confirmed preferably at the next scheduled visit and not less than 4 weeks after the visit when the response was last observed. There is no planned central review of scans.

This study will consist of a number of arms (sub-studies), each evaluating the efficacy, safety, and tolerability of a specific agent or combination.

At study commencement, there were 2 pre-defined arms:

A. Durvalumab (MEDI4736) + tremelimumab followed by durvalumab monotherapy

B. AZD1775 + carboplatin (CBDP)

A further arm was added in version 3

C. Ceralasertib (AZD6738) + olaparib.

Conduct of the study within these arms are detailed in Appendix A (Arm A), Appendix B (Arm B) and Appendix C (Arm C).

Study Objectives

Primary Objective:	**Outcome Measure:**
To assess the preliminary efficacy of each treatment arm in terms of ORR	ORR using Investigator assessments according to RECIST 1.1

Secondary Objective:	**Outcome Measure:**
To further assess the preliminary efficacy of each treatment arm in terms of DoR, DCR, TTR, PFS, and overall survival (OS)	DoR, DCR, TTR, and PFS using Investigator assessments according to RECIST 1.1 OS
To assess the pharmacokinetics (PK) of novel combination treatments (Arm A (stage 1 and 2 only), Arms B and C only)	Concentration of novel combination treatments in blood

Safety Objective:	**Outcome Measure:**
To assess the safety and tolerability profile of each treatment arm	Adverse events (AEs); physical examinations; vital signs, including blood pressure and pulse; electrocardiograms; and laboratory findings, including clinical chemistry, hematology, and urinalysis

CCI	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
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CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Target patient population

Male or female patients aged 18 years or older with histologically or cytologically documented extensive disease (American Joint Committee on Cancer Stage IV SCLC [T any, N any, M1 a/b]) at initial diagnosis and who have demonstrated PD either during first-line platinum-based chemotherapy (platinum refractory) or within 90 days of completing first-line platinum-based chemotherapy (platinum resistant), and a minimum life expectancy of 8 weeks. Patients should be enrolled within 90 days of progression in order to be accepted into the study. Refer to the specific sub-protocol for World Health Organization performance status requirements.

Duration of treatment

Unless specific treatment discontinuation criteria are met, all patients will continue therapy until disease progression.

Follow up of patients post discontinuation of study treatment

Patients who have discontinued treatment due to toxicity, symptomatic deterioration, or clinical progression, or who have commenced subsequent anticancer therapy, will be followed up until confirmed disease progression and for survival.

Survival

All patients will be followed monthly for survival for the first 3 months of the follow-up period and then every 2 months thereafter.

Investigational product, dosage and mode of administration

Specific information for each combination therapy arm are provided in the relevant sub-protocols Appendices (A, B and C). Additional information on the molecules is included from completed Phase I studies.

Summary of therapy arms in this version of the CSP:

ARM A

Patients enrolled in the durvalumab+ tremelimumab arm followed by the durvalumab monotherapy arm will receive

- Durvalumab 1500 mg + tremelimumab 75 mg via intravenous (IV) infusion every 4 weeks (q4w), starting on Week 0, for up to a total of 4 doses/cycles followed by durvalumab monotherapy 1500 mg via IV infusion q4w, starting 4 weeks after completion of the 4th cycle of combination therapy until PD, or for other discontinuation criteria. If a patient's weight falls to 30 kg or below (≤30 kg), then the patient should receive weight-based dosing after discussion between Investigator and Study Physician, until the weight improves to >30 kg, at which point the patient should start receiving the fixed dosing of durvalumab 1500 mg and tremelimumab 75 mg Q4W (during the combination phase of treatment). The equivalent weight based doses to the fixed doses are 20 mg/kg of durvalumab and 1 mg/kg tremelimumab Q4W.

ARM B

Patients enrolled in the AZD1775 + CBDP arm will receive

- AZD1775 225 mg twice daily (oral) for 2.5 days from Day 1 + CBDP area under the curve 5 (Day1) (IV); every 3 weeks

ARM C

Patients enrolled in the ceralasertib + olaparib arm will receive

- ceralasertib 160 mg QD PO between Days 1 to 7 + olaparib 300 mg BID PO between Days 1 to 28 days continuously; q4w until PD.

Statistical methods

The primary objective of this study is to assess the preliminary efficacy of each treatment arm in terms of ORR by Investigator assessment according to RECIST 1.1.

ORR (per RECIST 1.1 as assessed by site Investigator) is defined as the number (%) of patients with a confirmed CR or confirmed PR and will be based on all evaluable patients and will be estimated for each treatment arm with corresponding 2-sided 95% exact confidence intervals (CIs).

The table below shows the 2-sided exact 95% confidence intervals (CI) for the ORR of a treatment arm at each stage of the study, assuming the observed ORR is CCI% or CCI%:

ORR	**CCI%**	**CCI%**
Stage 1 (10 patients)	(CCI%, CCI%)	(CCI%CCI%)
Stage 2 (20 patients in total)	(CCI%, CCI%)	(CCI%, CCI%)
Expansion cohort (40 patients in total)	(CCI%, CCI%)	(CCI%, CCI5%)

Secondary efficacy variables include DoR, DCR, TTR, PFS, and OS. Efficacy data will be summarized and analyzed based on the Full Analysis Set.

An interim analysis will be conducted on each arm after stage 1 (first 10 patients). The Data cut off (DCO) for the interim analysis will take place approximately 12 weeks after the 10th eligible patient has initiated treatment. If there are CCI responders, then there is a low posterior probability of achieving ORR of at least CCI% in 20 patients and no further patients will be recruited to the arm. If there are CCI responders out of 10, then an additional 10 patients will be recruited and the final estimate of ORR will be based on 20 patients. If there are C or more responders out of 10 patients, then it will be regarded as strong efficacy and recruitment may be stopped in that specific arm. The posterior probability of having at leasCCI responders in 20 patients for CCI responders in 10 patients is shown below.

	CCI	CCI	CCI	CCI
CCI	CCI%	CCI CC	%	CCI %

If the decision is made to progress to stage 2 and treat a further 10 subjects in that arm, the primary analysis of ORR will occur approximately 12 weeks after the last patient in stage 2 has initiated treatment. All study endpoints will be analyzed at this time.

If the decision is made to close the Arm at the interim analysis the Sponsor will determine the appropriate length of follow up to ensure sufficient data collection for the primary analysis in that Arm.

If a decision is made to further expand any given arm (and treat a further 20 patients, to a maximum total of 40 eligible patients), the primary analysis of ORR will occur approximately 12 weeks after the last patient in the expansion group has initiated treatment. All study endpoints will be analyzed at this time.

Safety data will be evaluated on an ongoing basis and will be summarized descriptively and will not be formally analyzed.

All Review Committee decision making (including the decision whether to recommend opening Stage II or to expand the arm) will be based on the totality of the data available at the time, considering the benefit-risk assessment.

TABLE OF CONTENTS PAGE

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
AST	Aspartate aminotransferase
BRCA	Breast cancer susceptibility gene
CBDP	Carboplatin
CI	Confidence interval
CR	Complete response
CRF	Case report form (electronic/paper)
CSP	Clinical study protocol
CSR	Clinical Study Report
CT	Computed tomography
CCI	[redacted]
CCI	[redacted]
CTLA-4	Cytotoxic T-lymphocyte-associated antigen 4
CTCAE	Common Terminology Criteria for Adverse Event
CXCL	C-X-C motif ligand
DCO	Data cut off
DCR	Disease control rate
DDR	DNA damage repair
DILI	Drug-induced liver injury
DNA	Deoxyribonucleic acid
DoR	Duration of response
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group

Abbreviation or special term	Explanation
EDC	Electronic Data Capture
eCRF	Electronic case report form
ED	Extensive-stage disease
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose positron emission tomography
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HL	Hy's Law
IATA	International Airline Transportation Association
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IFN	Interferon
imAE	Immune mediated adverse event
IMP	Investigational Medicinal Product
International Coordinating Investigator	If a study is conducted in several countries the International Coordinating Investigator is the Investigator coordinating the Investigators and/or activities internationally.
IP	Investigational product
IRB	Institutional Review Board
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
NCI	National Cancer Institute
NE	Not evaluable
NSCLC	Non-small-cell lung cancer

Abbreviation or special term	Explanation
NTL	Non-target lesions
ORR	Objective response rate
OS	Overall survival
PARP	Poly(ADP-ribose) polymerase
PD	Progressive disease
PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
PET	Positron emission tomography
PFS	Progression-free survival
PHL	Potential Hy's Law
PK	Pharmacokinetic(s)
PR	Partial response
q4w	Every 4 weeks
QTcF	Heart rate corrected QT interval (Fridericia's formula)
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
SAE	Serious adverse event
SAP	Statistical analysis plan
SCLC	Small-cell lung cancer
SD	Stable disease
T3	Triiodothyronine
T4	Thyroxine
TBL	Total bilirubin
TIL	Tumor-infiltrating lymphocyte
TL	Target lesion
CCI	[redacted]
TSH	Thyroid-stimulating hormone
TTR	Time to response
ULN	Upper limit of normal
US	United States
WHO	World Health Organization

2. INTRODUCTION

2.1 Background and rationale for conducting this study

Small-cell lung cancer (SCLC) represents approximately 13% of all newly diagnosed lung cancers (Puglisi et al 2010). SCLC is perhaps the most aggressive form of the disease, distinguishable from non-small-cell lung cancer (NSCLC) by its rapid doubling time, high growth fraction, early dissemination, and frequent association with distinct paraneoplastic syndromes. It is strongly associated with tobacco smoking and is also associated with an extremely high mutation rate.

A 2-stage system dividing patients into limited and extensive-stage disease (ED) was developed in 1973 by the United States (US) Veteran's Administration Lung Cancer Study Group, and this is the most commonly employed system in clinical practice. Limited disease was defined as tumor tissue that could be encompassed in a single radiation port, and ED was defined as any tumor that extended beyond the boundaries of a single radiation port. At present, limited disease is identified in approximately 30% of patients, and ED is identified in approximately 70% of patients. Prognosis for patients with ED is poor; surgery is not usually an option in ED because of the inability of local excision to control systemic disease, leaving chemotherapy as the primary treatment modality. Without treatment, survival is a matter of weeks (Green et al 1969); with treatment, median overall survival (OS) is <10 months, and for patients with Stage IV disease, the 5-year survival rate is approximately 2% (FDA Guidance 2011, Foster et al 2011, Rossi et al 2012).

In terms of treatments, combination chemotherapies are the current standard of care for ED-SCLC and have remained largely unchanged for the past 2 decades. SCLC is highly responsive to first-line platinum-based chemotherapy. However, despite high initial response rates of up to 70% with a standard of 4 to 6 cycles of doublet chemotherapy (platinum + etoposide [ETOPOPHOS®]) (Rossi et al 2012), SCLC typically recurs within 1 year after treatment in the vast majority of patients (Ardizzoni 2004).

It is estimated that 80% of patients with limited stage and almost all patients with ED-SCLC relapse or experience disease progression (Clark and Ihde 1998). Most patients will relapse within 2 years and die from systemic metastases (Asai et al 2014).

Patients who receive a platinum-based treatment can be empirically divided into "refractory," "resistant," and "sensitive" on the basis of response to first-line chemotherapy (Califano et al 2012). Patients who have disease that progresses through first-line treatment are categorized as having refractory disease, while those who show initial response to treatment but whose disease progresses within 3 months of completing chemotherapy are categorized as having resistant disease. The sensitive subgroup includes those patients who have a relapse-free interval of at least 3 months from completion of treatment. The proportion of patients with refractory, resistant, and sensitive disease is approximately 20%, 35%, and 45%, respectively. Despite this classification of patients with refractory, resistant, and sensitive disease, in clinical studies, the term "refractory" has been used to include patients who have disease that progresses through first-line treatment and those who show an initial response to treatment but

whose disease progresses within 3 months of completing chemotherapy (ie, refractory and resistant).

Single-agent topotecan (HYCAMTIN®; both intravenous [IV] and oral formulations) is the only drug approved as second-line treatment for recurrent SCLC in the US, European Union (EU), and Japan (IV formulation only in Japan). Amrubicin (CALSED®) is also approved for use in Japan but currently not in any other country. It is important to note that while there have been multiple studies to underpin the approval of topotecan in patients with sensitive disease, the approval for topotecan for patients with refractory disease is based on 1 single study where the comparator arm was best supportive care (O'Brien et al 2006). In this study, topotecan was shown to extend survival from 13.9 to 25.9 weeks with greater symptom control.

A recent meta-analysis of more than 1300 SCLC patients treated with topotecan concluded that topotecan treatment in patients with refractory disease (classed as progression that occurs within 90 days post completion of first-line chemotherapy, ie, both refractory and resistant disease) is associated with poor outcomes; pooled analysis reported objective response rate (ORR) of 5% and a 12-month survival rate of just 9% (Horita et al 2015). Treatment is often associated with significant hematological toxicity (~69% patients experience Grade 3/4 neutropenia, as an example), calling into question the true benefit:risk assessment for this treatment option.

A number of targeted agents have been investigated in SCLC, mostly in unselected populations, but with disappointing results (Asai et al 2014).

There remains a significant unmet medical need for patients with refractory/resistant ED-SCLC; as highlighted above, approximately 95% of patients fail to respond to single-agent topotecan, which is the only currently approved available treatment in most countries.

The mechanisms that underpin the high rate of relapse in SCLC are still poorly understood; the disease's rapid progression and the lack of available tissue for translational research mean that there has been little progress in this area. If focus is placed on the available information that SCLC is associated with high mutation burden and genomic instability together with data to suggest enhanced deoxyribonucleic acid (DNA) repair mechanisms could be a resistance mechanism (Tapia and DiazPadilla- 2013), it can be hypothesized that agents that harness the immune system together with agents that affect DNA repair could prove beneficial in this disease setting. As such, this umbrella study aims to test multiple agents that fall into 2 main categories, ie, those that harness the immune system and those that affect DNA repair.

SCLC is also an ideal clinical setting for the exploratory study of the evolution of tumor genetics in patients with SCLC because the high levels of CCI [redacted] in this tumor histology are both prognostic (Huang et al 2014) and allow genetic analysis through "liquid biopsies" (Hodgkinson et al 2014).

Novel therapies are needed to improve clinical outcomes in both extending survival for those patients who initially respond to treatment with chemotherapy, as well as those who ultimately progress following treatment with chemotherapy.

2.1.1 Immunotherapies

It is increasingly understood that cancers are recognized by the immune system, and, under some circumstances, the immune system may control or even eliminate tumors (Du Bois et al 2003, Dunn et al 2004). The connection between cancer and the immune system was first uncovered nearly 100 years ago, long before an in-depth knowledge of the intricate workings of the immune system existed (Cancer Research Institute 2003). Failure of immune surveillance of preneoplastic lesions and micrometastases is a key step in cancer development. Individuals with chronic immunosuppression show higher rates of cancer. This observation led to the hypothesis that sporadic cancers among immunocompetent individuals are likely to be minimally immunogenic, allowing for passive escape from immune surveillance. Recent data suggest that this may be an oversimplification. Some sporadic tumors are highly immunogenic but actively suppress the local immune environment through the production of immunosuppressive cytokines (Shields et al 2010). As such, the local tumor environment is likely a highly dynamic environment where most tumors grow and metastasize through adaptive responses that modulate antitumor immunity.

The complexity and redundancy of the immune system offer multiple targets that may be manipulated to maximize the body's inherent immune response to a tumor. This immune response may be augmented by direct stimulation of effector cells, increased antigen presentation leading to indirect stimulation of effector cells, or blockade of immunosuppressive factors or cells (Monti et al 2005).

Tumor-infiltrating lymphocytes (TILs) have the capacity to control the growth of many types of cancers (Gooden et al 2011). Most tumors show infiltration by TILs, but tumors modulate the local microenvironment through surface expression or release of inhibitory molecules. Engagement of TIL cell surface receptors with these inhibitory ligands leads to a dysfunctional immune response, causes T-cell exhaustion, and facilitates tumor progression (Baitsch et al 2012, Crespo et al 2013). Novel monoclonal antibodies (mAbs) that block these inhibitory receptors have shown significant clinical activity across a number of tumor types (Brahmer et al 2010, Hodi et al 2010, Robert et al 2011, Topalian et al 2012, Wolchok et al 2009). Specifically, blockade of immune checkpoint signaling (through cytotoxic T-lymphocyte-associated antigen 4 [CTLA-4], programmed cell death 1 [PD-1], and programmed cell death ligand 1 [PD-L1]) has shown clinical activity not only in conventionally immune-responsive tumors, such as melanoma and renal cell carcinoma, but also in NSCLC (Brahmer et al 2010, Brahmer et al 2012, Topalian et al 2012), prostate cancer (Harzstark and Small 2010, Slovin et al 2013), mesothelioma (Calabrò et al 2013), and other solid tumors (Brahmer et al 2010, Brahmer et al 2012, Gordon et al 2013).

2.1.2 Immunotherapies in SCLC

During the last decade, there has been a progressively increased interest in studying the therapeutic potential of immunotherapies for different types of tumors. In particular,

nonclinical and clinical studies have indicated that blockade of immune checkpoints (PD-1/PD-L1 and CTLA-4) can have a positive effect on antitumor immunity. One potential strategy is to combine these non-redundant and potentially synergistic single-agent immunotherapies together, thereby producing an additive improvement in tumor response (Larkin et al 2015, Postow et al 2015).

Patients with SCLC may be particularly susceptible to immunotherapies given the high mutational burden of this disease (SCLC has the 5th highest level of mutations of all human cancers; Alexandrov et al 2013) and the likely high antigen release following the responses that are often observed in this indication with frontline chemotherapy. SCLC is associated with multiple mutations in oncogene and tumor-suppressor pathways, the most prevalent being almost universal loss of tumor protein 53 and retinoblastoma protein (Salgia and Skarkin 1998). Such abnormalities predispose the tumor to uncontrolled proliferation, reduced apoptosis, and a reliance on DNA damage repair (DDR) pathways. In addition to these mutations, chromosomal abnormalities are found in the majority of patients with SCLC, and microsatellite instability is also common (Merlo et al 1994, Chen et al 1996). As such, SCLC presents with a high degree of genomic instability and chromosomal abnormality (Massari et al 2015). Genomic instability, driven by mismatch repair deficiency, has been shown in recent studies to be a potential driver of response to checkpoint inhibition (Le et al 2015), likely because such deficiency leads to high mutational burden. Several recent studies analyzing data from different tumor types have demonstrated a correlation between mutational burden and response to checkpoint inhibitors targeting both PD-1 (Rizvil 2015) and CTLA-4 (Snyder et al 2014, Van Allen et al 2015).

Although no such correlative studies have included SCLC, given the high mutational load and genomic instability seen in these tumors, one can hypothesize that this same class of agents would also prove beneficial in this disease setting.

This is supported by encouraging clinical activity reported with this class of agents in both first-line and second-line settings in patients with SCLC, both as monotherapy and in combination. Recent studies, specifically in the platinum refractory/resistant SCLC setting, have also shown promise. The ongoing KEYNOTE-028 study (NCT02054806) has recently reported that pembrolizumab (KEYTRUDA®; anti-PD-1 mAb) showed 35% ORR and 40% disease control rate (DCR) in patients with PD-L1-positive, recurrent SCLC. Responses appear to be durable, with 6 out of 7 responders ongoing as of March 2015 (Ott et al 2015). Nivolumab (OPDIVOR®) as monotherapy or in combination with ipilimumab (YERVOY®; anti-CTLA-4 mAb) has also been investigated in relapsed SCLC, with preliminary promising results of 18% and 32.6% ORR, respectively. Furthermore, DCR was 38% for nivolumab as monotherapy versus 54% for nivolumab in combination with ipilimumab. Median survival data have also been recently reported in this study; nivolumab alone had an OS of 4.4 months (n=40) versus 8.2 months (n=46) for nivolumab in combination with ipilimumab (Antonia 2015). Taken together, these preliminary data are very encouraging when comparing to pooled analysis for single-agent topotecan, which demonstrated a typical ORR of 5% and a 12-month survival rate of 9% (Horita et al 2015) in this refractory setting.

AstraZeneca is also investigating the use of durvalumab + tremelimumab combination therapy for the treatment of cancer. The development of durvalumab in combination with tremelimumab was initiated in Study D4190C00006 (NSCLC) and Study D4190C00010 (in a range of tumor types, including SCLC). Preliminary data from these studies suggested that this CCI [redacted] Based on CCI [redacted] from these studies, further exploration of the benefit/risk of the durvalumab + tremelimumab combination therapy in SCLC is warranted.

2.1.3 DNA damage and repair mechanisms in SCLC

Although exact mechanisms of drug resistance remain to be elucidated, it seems to be a multi-factorial process with pivotal roles for altered expression of genes encoding proteins involved in drug transport and DDR mechanisms. Moreover, clinically observed platinum resistance (in ovarian carcinoma) is associated with 1) decreased cellular accumulation of drug in tumor cells, 2) augmented drug inactivation, 3) increased DNA repair, and 4) tolerance to DNA damage (Kurzeder et al 2006).

Proteomic profiling across >30 SCLC cell lines and 12 primary SCLC tumors has identified high expression of E2F transcription factor 1-regulated proteins, including enhancer of zeste homolog 2, DNA repair and apoptosis proteins, and poly(ADP-ribose) polymerase (PARP) 1 as potential targets in SCLC based on their differential dysregulated expression (Byers et al 2012). Given the similarity of SCLC to ovarian carcinoma in terms of initial sensitivity to platinum and the proven clinical utility of PARP inhibitors in that setting, this study further explored the effects of PARP inhibition on SCLC cell lines. They found that they were as sensitive as breast cancer susceptibility gene (BRCA)-mutated breast and ovarian cell lines, and that sensitivity was correlated with increased expression of PARP (Wainberg et al 2014) Recently they have presented the first clinical evidence of a single-agent PARP inhibitor in platinum-resistant SCLC with BMN673 with initial data from 25 patients demonstrating a 25% DCR (complete response [CR] + partial response [PR] + stable disease [SD] >24weeks).

Taken together, there may be a role for agents that inhibit DNA repair in SCLC.

2.1.4 DNA damage and immunogenicity

Accumulating DNA damage has the potential to modify the immunogenicity of tumors through a number of key mechanisms:

Triggering of intracellular signaling events that result in the activation of nuclear factor kappa B and interferon (IFN) regulatory factor 7. These transcriptional regulators result in the increased production of cytokines and chemokines that have the potential to promote antitumor immunity, such as type I IFNs (Chatzinikolaou et al 2014).

Upregulation of surface receptors such as major histocompatibility complex, ligands for natural-killer group 2, member D, and inducible T-cell costimulatory ligand, which render tumor cells more visible to detection by cytotoxic T cells (Tang et al 2014).

Death of tumor cells and release of antigen, which may help to promote antigen presentation and immune priming (Kroemer et al 2012).

These effects would be expected to help promote an effective antitumor immune response. In keeping with this hypothesis, several tumor types with genetic defects expected to lead to increased DNA damage show evidence of enhanced immune recognition. For example, BRCA tumor cells are associated with higher levels of TILs and secreting lymphocyte attractants (eg, C-X-C motif ligand [CXCL] 10) and immune-suppressive ligands such as PD-L1 (Mulligan et al 2014). Similarly, ataxia telangiectasia mutated-negative gastric tumors are associated with higher levels of microsatellite instability, which is itself associated with higher response rates to immunotherapy in colorectal cancer (Kim et al 2014, Le et al 2015).

Similarly, modification of the pathways involved in controlling DNA damage through use of selective inhibitors has been shown to have beneficial effects on the immune system non-clinically. For example, Wee1 inhibition, through AZD1775, has been demonstrated to increase the capacity of T cells to induce tumor cell lysis (Hamilton et al 2014), while PARP inhibition has been shown to synergize with CTLA-4 blockade and promote release of IFNγ in a mouse model of BRCA-deficient ovarian cancer (Higuchi et al 2015).

2.2 Rationale for study design, doses, and control groups

2.2.1 Rationale for study design

This is an exploratory, signal-searching study with multiple arms with a primary endpoint of ORR. Experimental arms may open concurrently and recruit up to 40 eligible patients.

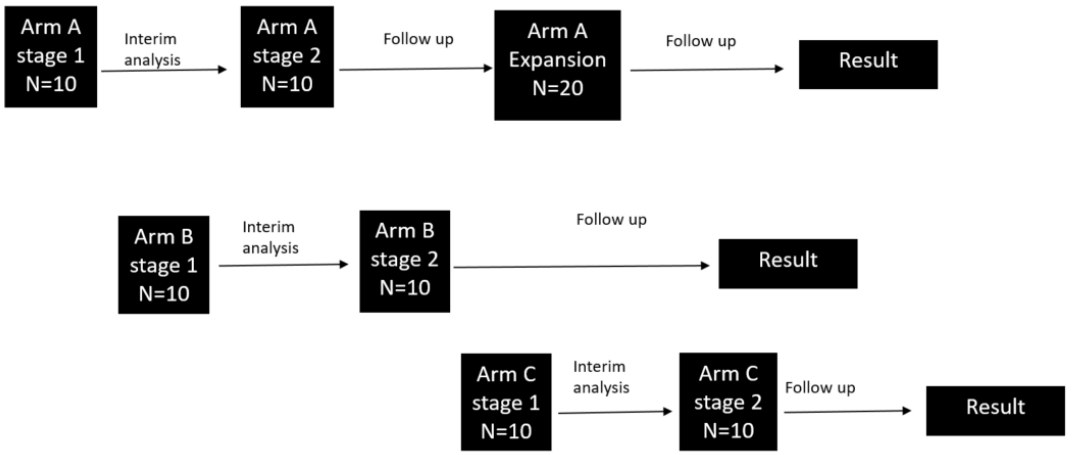
Enrollment into any given arm on the study will be sequential and follow a staged design; each arm will initially enroll a minimum of 10 patients (see Figure 1 Staged recruitment design). After the initial 10 eligible patients are treated on each arm and assessed for a minimum of 12 weeks, an interim analysis will be performed, which will determine whether recruitment should expand to the second stage (an additional 10 patients for a total of 20 patients) for that specific arm or stop. The Sponsor Review Committee (see Section 7.9) may decide to enroll additional patients to replace any patients who do not meet the key inclusion criteria at each stage. If the results of the primary ORR analysis from the completed 2nd stage of any arm are encouraging the Review Committee could decide to recommend adding up to an additional 20 eligible subjects (for a total of 40 eligible patients) into an expansion cohort to further explore the findings.

All Review Committee decision points (including the decision whether to recommend opening Stage II or to expand the arm) will be based on the totality of the data available at the time, considering the benefit-risk assessment.

This design allows rapid assessment of a given treatment by directly measuring the treatment effect on the tumor with no/minimal impact on enrollment to the study overall. As discussed in Section 2.1, the response rate in the refractory/resistant setting for ED-SCLC is poor with current therapies. The interim assessment of efficacy in 10 patients not only facilitates an early stop if patients are deriving no benefit (e.g. 0/10 responses) but could also prompt early

closure if promising efficacy is observed (≥3/10 responses). For more details on the proposed interim analysis, see Section 9.5.7.

Figure 1 Staged recruitment design



This study was opened with 2 arms initially (A and B) and was amended with version 3 to add Arm C in the original modular design where multiple treatment arms of novel combination therapies can be added and opened. Each new therapy will have a defined dose and schedule based on earlier studies investigating that combination, as well as a clear rationale for the expected efficacy in this setting. Please refer to each specific arm(s) for this information.

2.2.2 Rationale of the study for specific agents

Please see specific study arm appendices for rationale on specific agents.

- Appendix A: Arm A (durvalumab + tremelimumab followed by durvalumab monotherapy)
- Appendix B: Arm B (AZD1775 + carboplatin [CBDP])
- Appendix C: Arm C (AZD6738 + olaparib)

2.2.3 Rationale for study endpoints

The primary aim of this study is to determine the preliminary efficacy of novel combinations of anti-cancer agents in patients with refractory or resistant ED-SCLC. The primary endpoint of the study is ORR by Investigator assessment according to Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1). ORR measures direct effects on tumors and has been widely used as the endpoint in early clinical development for decades. A meta-analysis of 14 studies in 12567 patients with advanced NSCLC submitted to the Food and Drug Administration (FDA) between 2003 and 2013 demonstrated a strong patient-level association

between response and progression-free survival (PFS) and OS (Blumenthal et al 2015). The FDA has used ORR as the endpoint for accelerated approval of breakthrough novel therapies.

2.2.4 Background, rationale, and risk benefit information on specific agents

See the following appendices for information on specific agents and the scientific rationale supporting the combinations for investigation in each arm:

- Appendix A: Arm A (durvalumab + tremelimumab followed by durvalumab monotherapy):
- Appendix B: Arm B (AZD1775 + carboplatin [CBDP])
- Appendix C: Arm C (AZD6738 + olaparib)

2.3 Benefit/risk and ethical assessment

As described in Section 2.1, the prognosis of refractory or resistant SCLC is very poor. Single-agent topotecan is the only drug approved as second-line treatment for recurrent SCLC in most countries. A meta-analysis has shown that topotecan has limited activities in this setting, with an ORR of 5%, 6 month OS rate of 37% and 12 month OS rate of 9% (Horita et al 2015). Therefore, there is a significant unmet medical need for improving treatment outcome and provide more treatment options to patients with refractory or resistant ED-SCLC.

The benefit/risk and ethical assessments that are specific to each arm of the Clinical study protocol (CSP) are described in the relevant section of each specific arm appendix.

The monitoring and management of the potential risks are discussed in Section 7. Refer to the relevant Investigator's Brochure (IB) and arm for each agent used for more information on the potential benefits of each agent and an assessment of the potential and known risk.

2.3.1 Summary benefit/risk statement

There remains a significant unmet medical need for patients with refractory/resistant ED-SCLC; as highlighted above, approximately 95% of patients fail to respond to single-agent topotecan, which is the only currently approved available treatment in most countries.

The mechanisms that underpin the high rate of relapse in SCLC are still poorly understood; the disease's rapid progression and the lack of available tissue for translational research mean that there has been little progress in this area.

The study design aims to minimize potential risks in several ways. Firstly, by minimizing the number of subjects exposed to study drugs, via the staged recruitment process. Second, the protocol includes safety monitoring in excess of standard of care monitoring, with the intent of protecting subjects involved in the study. Furthermore, there is specific guidance for Investigators for each arm to support optimal management of those risks deemed to be most

likely or serious. Potential benefits of each combination in patients with refractory/resistant ED-SCLC are unknown at this time; however, non-clinical and clinical data to date have showed acceptable safety profile and anti-tumor activity for the agents proposed in this study (see specific sub-protocol Appendices for more information).

Thus, the benefit/risk assessment for this Phase II study is acceptable.

2.4 Study design

This is a Phase II, open-label, multi-drug, multi-center, multi-arm study to determine the preliminary efficacy of novel combinations of treatment in patients with ED-SCLC who have refractory or resistant disease, defined as patients who progress during first-line platinum-based chemotherapy or those who progress within 90 days after completing first-line platinum-based chemotherapy.

This multi-arm study initially opened with 2 arms (Arms A and B), and an additional arm (Arm C) was added in version 3;additional arms may be opened provided there is compelling rationale for the combination and a safe and tolerable dose and schedule have been determined from ongoing Phase I studies (Figure 2).

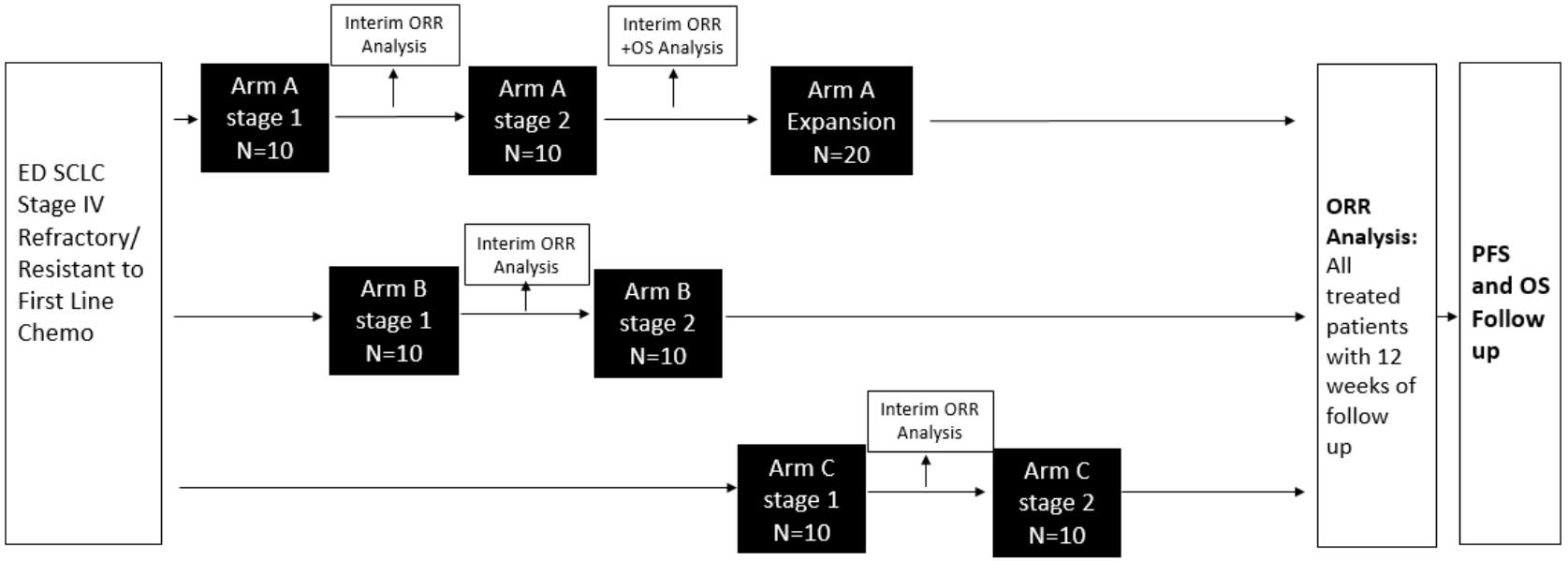
The 3 experimental arms are:

- Arm A (durvalumab + tremelimumab followed by durvalumab monotherapy) - Appendix A
- Arm B (AZD1775 + CBDP) -Appendix B
- Arm C (AZD6738 + olaparib) - APPENDIX C

Each arm will have its own sub-protocol to include study information specific to that arm.

Each arm is independent, and any signal observed in 1 arm will not have an impact on the other arm in the study. Please refer to each sub-study appendix for the relevant study flowchart.

Figure 2 Overall study design



ED-SCLC Extensive-stage disease small-cell lung cancer; ORR Objective response rate; OS Overall survival; PFS Progression-free survival.

3. STUDY OBJECTIVES

All objectives will be evaluated for all patients, unless otherwise indicated. Please also refer to relevant sub-protocol appendix for objectives applicable to particular arm of the study (eg, Appendix A for Arm A).

3.1 Primary objective

Primary Objective:	**Outcome Measure:**
To assess the preliminary efficacy of each treatment arm in terms of ORR	ORR using Investigator assessments according to RECIST 1.1

3.2 Secondary objectives

Secondary Objective:	**Outcome Measure:**
To further assess the preliminary efficacy of each treatment arm in terms of duration of response (DoR), DCR, time to response (TTR), PFS, and OS	DoR, DCR, TTR, and PFS using Investigator assessments according to RECIST 1.1 OS
To assess the pharmacokinetics (PK) of novel combination treatments (Arm A, stages 1 and 2 only, Arm B and Arm C)	Concentration of novel combination treatments in blood

3.3 Safety objectives

Safety Objective:	**Outcome Measure:**
To assess the safety and tolerability profile of each treatment arm	Adverse events (AEs); physical examinations; vital signs, including blood pressure and pulse; electrocardiograms (ECGs); and laboratory findings, including clinical chemistry, hematology, and urinalysis

3.4 Exploratory objectives

CCI [redacted]	[redacted]
[redacted]	[redacted]

CCI	

CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

4. PATIENT SELECTION, ENROLMENT, RANDOMIZATION, RESTRICTIONS, DISCONTINUATION, AND WITHDRAWAL

Each patient must meet all of the sub protocol inclusion criteria and exclusion criteria for this study. Please refer to Appendix A, B or C for inclusion/exclusion criteria specific to each individual arm of the study.

4.1 Inclusion criteria

Please refer to Appendix A (Arm A Inclusion criteria), B (Arm B Inclusion criteria) or C (Arm C inclusion criteria) for inclusion criteria for each individual arm of the study.

4.2 Exclusion criteria

Please refer to Appendix A (Arm A Exclusion criteria), B (Arm B Exclusion criteria) or C (Arm C Exclusion criteria) for exclusion criteria for each individual arm of the study.

4.3 Patient enrollment and randomization

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

At screening/baseline (Days -28 to -1), the Principal Investigator, or suitably trained delegate, will:

1. Obtain signed informed consent from the potential patient or their guardian/legal representative before any study-specific procedures are performed. If laboratory or imaging procedures were performed for alternate reasons prior to signing consent, these can be used for screening purposes with consent of the patient. However, all screening laboratory and imaging results must have been obtained within 28 days of enrollment.

2. Obtain a unique 7-digit enrollment number (E-code) through the Interactive Voice Response System (IVRS)/Interactive Web Response System (IWRS) into the following format "E#".

3. Determine patient eligibility. See Section 4 and specific treatment sub-protocol (please check the specific arm appendix for details).

Patients will begin treatment on Day 1. Patients must not be treated unless all eligibility criteria have been met.

There is no randomization in the study.

If a patient withdraws from participation in the study, then his or her enrollment code cannot be reused, and they cannot re-enter the study. Withdrawn patients will not be replaced.

4.4 Procedures for handling incorrectly enrolled or randomized patients

Patients who fail to meet the eligibility criteria must not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Patients who are enrolled but subsequently found not to meet all the eligibility criteria must not be initiated on treatment and must be withdrawn from the study.

When a patient is started on study treatment and is later found to not meet all the eligibility criteria (e.g. during routine monitoring), the Investigator should inform the AstraZeneca Study Physician immediately. A discussion should occur between the AstraZeneca Study Physician and the Investigator regarding whether to continue or discontinue the patient from treatment based on risk/benefit assessment. The AstraZeneca Study Physician must ensure all decisions are appropriately documented.

4.5 Methods for assigning treatment groups

At baseline, patients who satisfy all the inclusion and exclusion criteria to participate in a particular treatment arm will be enrolled sequentially in that treatment arm. If they do not fulfil the criteria for one arm but satisfy all the criteria for another ongoing arm of the study then they may be enrolled into the arm for which they are most suitable.

Every effort should be made to minimize the time between enrollment and starting study treatment.

Patients cannot enroll into more than 1 arm. For example, if a patient is enrolled into Arm A and experiences PD, he or she cannot enroll into another sub-study of this protocol.

4.6 Methods for ensuring blinding

Not applicable, as study is open label.

4.7 Methods for unblinding

Not applicable, as study is open label.

4.8 Restrictions

Please refer to the specific sub-study appendix (eg, Appendix A for Arm A) for specific restrictions applicable to each arm of the study.

4.9 Discontinuation of investigational product

An individual patient will not receive any further IP if any of the following occur in the patient in question:

- Withdrawal of consent from further treatment with IP. The patient is, at any time, free to discontinue treatment, without prejudice to further treatment. A patient who discontinues treatment is normally expected to continue to participate in the study unless they specifically withdraw their consent to further participation in any study procedures and assessments (see Section 4.10.2).
- Any AE that meets criteria for discontinuation as defined in the Dosing Modification and Toxicity Management Guidelines (see study-specific information in sub-protocols). Note that this is arm specific; this would not impact enrollment into the other arms in the study.
- Initiation of alternative anticancer therapy including another investigational agent.
- AEs that, in the opinion of the Investigator or the Sponsor, contraindicate further dosing. Note that this is arm specific; this would not impact enrollment into the other arms in the study.
- Confirmed PD per RECIST 1.1 and Investigator determination that the patient is no longer benefiting from treatment with IP.
- Non-compliance with the study protocol that, in the opinion of the Investigator or AstraZeneca, warrants withdrawal from treatment with IP (eg, refusal to adhere to scheduled visits).
- Patients incorrectly initiated on study treatment (eg, patient is determined to have met 1 or more of the exclusion criteria for study participation at study entry and continuing investigational therapy might constitute a safety risk)
- Pregnancy or intent to become pregnant.

Should any of this occur, the patient will not receive any further IP.

If the patient is discontinued from study treatment, the scheduled study visits, data collection, and procedures should continue according to this study protocol until study closure of the arm the patient is participating in. Alternatively, if the patient does not agree to this option, a modified follow-up through methods such as regular telephone contacts or a contact at study closure should be arranged, if agreed to by the patient and in compliance with local data privacy laws/practices (see Section 4.9.2).

4.9.1 Procedures for discontinuation of a patient from investigational product

At any time, patients are free to discontinue IP without prejudice to further treatment. A patient who decides to discontinue IP will always be asked about the reason(s) for discontinuation and the presence of any AEs. If possible, they will be seen and assessed by an Investigator(s). AEs will be followed up (see Section 7). The AstraZeneca Study Physician should be notified of any ongoing AE that may delay treatment or necessitate permanent discontinuation of treatment.

Patients who are permanently discontinued from further receipt of IP, regardless of the reason, will be identified as having permanently discontinued treatment. Patients who are permanently discontinued will enter the follow-up period (see specific arm appendix for details).

All patients will be followed for survival until the end of the study.

Patients who decline to return to the site for evaluations should be contacted by telephone as an alternative.

Any patient who discontinues study treatment for reasons other than objective disease progression should have tumor assessments performed as scheduled until confirmed objective disease progression is documented or death occurs, unless consent is withdrawn.

Patients who have permanently discontinued from further receipt of IP will need to be discontinued from the IVRS/IWRS.

If a patient is withdrawn from the study, see Section 4.10.

4.9.2 Assessments following discontinuation of investigational product

Patients who are permanently discontinued from receiving IP will remain in the study and will be followed per the study plan (see the relevant arm sub-protocol) for safety, including the collection of any protocol-specified blood specimens, unless consent is withdrawn or the patient is lost to follow-up or enrolled in another clinical study. All patients will be followed for survival (please see follow-up tables for each specific study arm). Patients who decline to return to the site for evaluations will be offered follow-up by phone. However, patients who discontinue due to an AE will need to attend all protocol-specified visits, and all assessments will be conducted as scheduled.

All patients who have any Grade 3 or 4 laboratory values at the time of discontinuation must have further tests performed, and the results must be recorded on the appropriate electronic case report form (eCRF) until the laboratory values have returned to Grade 1 or 2, unless these values are not likely to improve because of the underlying disease.

At discontinuation, all ongoing study-related toxicities and serious adverse events (SAEs) must be followed until resolution unless, in the Investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease.

All SAEs occurring for up to the pre-defined time period after the last dose of study treatment must be recorded in the eCRF. See the relevant appendices for the pre-defined time period for collection of SAEs for specific agents.

Drug- or study procedure-related SAEs must be captured until the patient completes the follow-up period following discontinuation of study drug (due to confirmed progression of disease) or is permanently withdrawn from the study. Both the patient and the physician will be asked about the subsequent treatment the patient receives during the follow-up period per the study plan.

4.10 Criteria for withdrawal

4.10.1 Screen failures

Screen failures are patients who do not fulfil the eligibility criteria for the study, and therefore must not be treated with study drug or progress any further on the study. These patients should have the reason for study withdrawal recorded as "eligibility criteria not fulfilled" (ie, patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (not enrolled patients who commence on study treatment). Patients are not allowed to be rescreened.

4.10.2 Withdrawal of the informed consent

Patients are free to withdraw from the study at any time (IP and assessments) without prejudice to further treatment.

Patients who withdraw consent for further participation in the study will not receive any further IP or further study observation, with the exception of follow-up for survival, which will continue until the end of the study unless the patient has expressly withdrawn their consent to survival follow-up. Note that the patient may be offered additional tests or tapering of treatment to withdraw safely.

A patient who withdraws consent will always be asked about the reason(s) and the presence of any AE. If possible, they will be seen and assessed by an Investigator. The Investigator will follow up AEs outside of the clinical study.

If a patient withdraws from participation in the study, then his or her enrollment code cannot be reused. Withdrawn patients may be replaced following discussion between AstraZeneca Study Physician and AstraZeneca Study Statistician.

If consent is withdrawn, the patient will not receive any further study treatment or further study observation. The patient will be specifically asked if they are withdrawing consent to:

- Further participation in the study including any further follow-up (eg, survival calls)
- Withdrawal of consent to the use of their study-generated data
- Withdrawal to the use of any samples

Note that the patient may be offered additional tests or tapering of treatment to withdrawal for safety and will be offered follow-up by phone. If a patient wishes to withdraw their consent to further participation in the study, including survival follow-up (by phone), this should be clearly documented in the patient notes and in the clinical study database.

Regardless of the reason for termination, all data available for the patient up to the time of discontinuation of follow-up must be recorded in the eCRF. All reasons for discontinuation of treatment must be documented.

4.10.3 Survival status for withdrawn consent and lost to follow-up patients

In order to support key end points of PFS and OS analyses, the survival status of all patients in the full analysis and the safety analysis sets should be re-checked. This includes those patients who withdrew consent or are classified as "lost to follow up."
• Lost to Follow up: site personnel should check hospital records, the patients' current physician, and a publicly available death registry (if available) to obtain a current survival status in the 7 days following data cutoff. (The applicable CRF modules will be updated.)
• In the event that the patient has actively withdrawn consent to the processing of their personal data, the survival status of the patient can be obtained by site personnel from publicly available death registries (if available) where it is possible to do so under applicable local laws to obtain a current survival status in the 7 days following data cutoff. (The applicable CRF modules will be updated.)

Patients will be considered lost to follow-up only if no contact has been established by the time the study is completed such that there is insufficient information to determine the patient's status at that time.

Note: Patients who refuse to continue all participation in the study, including study team phone contact with their clinician to obtain follow up, should be documented as "withdrawal of consent" rather than "lost to follow-up."

Investigators should document attempts to re-establish contact with missing patients throughout the study period. If contact with a missing patient is re-established, the patient should not be considered lost to follow-up and any evaluations should resume according to the protocol.

4.11 Discontinuation of the study

Specific arms in this study may be stopped if, in the judgment of AstraZeneca, study patients are placed at undue risk because of clinically significant findings that meet any of the following criteria:

- Meet individual stopping criteria or are otherwise considered significant.
- Are assessed as causally related to study drug.
- Are not considered to be consistent with continuation of the study.

Note that this is arm specific; this would not impact enrolment into the other arms in the study as each arm would be considered separately.

In terminating any particular sub-study, or the entire study, the Sponsor will ensure that adequate consideration is given to the protection of the patients' interests.

5. STUDY PLAN AND TIMING OF PROCEDURES

The study plan for each arm of the study will be included in the appropriate arm appendix. Please consult the appendix for the sub-study in which patients are enrolled (eg, Appendix A for Arm A). See Figure 2 for the study flow chart.

For all treatment arms

- Tumor efficacy (RECIST) assessment dates are not affected by dose delays and remain as originally scheduled, as they are based on the date of initiation of study therapy.
- All other scheduled assessments must be performed relative to the start of the dosing cycle such that all laboratory procedures, etc required for dosing should be performed within 3 days prior to dosing. See individual arm appendix for details of all scheduled assessments.

6. STUDY ASSESSMENTS

A Web-Based Data Capture system will be used for data collection and query handling. The Investigator will ensure that data are recorded on the eCRFs as specified in the study protocol and in accordance with the instructions provided.

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

The study assessments described here are applicable to all arms in the study. Please refer to the corresponding sections of each specific modular appendix (eg, Appendix A for Arm A) for study assessments that are specific to each arm of the study.

6.1 Efficacy assessments

This study will evaluate the primary endpoint of ORR as determined by Investigator assessment according to RECIST 1.1 criteria. Efficacy assessments of PFS, TTR, DoR, and DCR will be derived (by AstraZeneca) using Investigator RECIST 1.1 assessments. In addition, OS will be determined as a secondary efficacy endpoint.

Tumor assessments use images from CT (preferred) or MRI, each preferably with IV contrast, of the chest, abdomen, and pelvis, collected during screening/baseline and at regular (follow-up) intervals during study treatment. Any other areas of disease involvement should be additionally imaged based on the signs and symptoms of individual patients.

The RECIST 1.1 guidelines (Appendix F) provide a method of assessment of change in tumor burden in response to treatment. Screening/Baseline imaging should be performed no more than 28 days before start of study treatment and ideally should be performed as close as possible to and prior to the start of study treatment. The RECIST 1.1 assessments of baseline images identify target (defined and measurable) and non-target lesions. Each lesion (and any new lesion) is evaluated in subsequent on-treatment follow-up images. This allows determination of follow-up target lesion response, non-target lesion response, and overall timepoint tumor responses (CR, PR, SD, PD, or not evaluable [NE]).

Efficacy for all patients (all arms) will be assessed on images collected either every 6 or 8 weeks ± 1 week until confirmed objective disease progression or when the patient has been taken off-study. It is important to follow the assessment schedule as closely as possible (refer to the study plans in each arm [screening and treatment period, and follow-up]). If an unscheduled imaging assessment is performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at his or her next regularly scheduled imaging visit.

According to RECIST 1.1, objective tumor response (CR or PR) should be confirmed preferably at the next scheduled imaging visit and not less than 4 weeks after the visit when the response was last observed.

Patients who have discontinued treatment due to toxicity or symptomatic deterioration, clinical progression, or who have commenced subsequent anticancer therapy will be followed up with tumor assessments until RECIST 1.1-defined PD or until death (whichever comes first) and followed for survival.

For the immunotherapy arm only, a follow-up scan is requested following an overall timepoint assessment of progression by RECIST 1.1, preferably at the next scheduled imaging visit and no earlier than 4 weeks after the previous assessment of PD in the absence of clinically significant deterioration. Treatment will continue between the initial assessment of

progression and confirmation for progression. If a patient discontinues treatment (and/or receives a subsequent anticancer therapy) after the initial assessment of progression, then the patient should continue to be followed with scheduled imaging until confirmed objective disease progression.

It is important to follow the assessment schedule as closely as possible. Please refer to the study plan of the relevant arm appendix.

6.1.1 Survival assessments

Following treatment discontinuation, assessments for survival must be made monthly for the first 3 months and then every 2 months thereafter. Survival information may be obtained via telephone contact with the patient or the patient's family, or by contact with the patient's current physician. The details of first and subsequent therapies for cancer, after discontinuation of treatment, will be collected.

In addition, patients on treatment or in survival follow-up will be contacted following the data cut-off for the primary analysis and all subsequent survival analyses to provide complete survival data. These contacts should generally occur within 7 days after the data cut-off.

6.2 Safety assessments

6.2.1 Laboratory safety assessments

Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis will be taken at the times indicated in the study plan (see the specific section of the relevant arm appendix). Please also refer to the Laboratory Manual.

Clinical laboratory safety tests, including serum pregnancy tests, will be performed in a licensed clinical laboratory according to local standard procedures. Sample tubes and sample sizes may vary depending on the laboratory method used and routine practice at the site. Pregnancy tests may be performed at the site using a licensed test (urine or serum pregnancy test). Clinically significant abnormal laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).

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

Laboratory tests do not need to be repeated at baseline if the baseline visit is within 3 days of the screening sample. The date of each collection will be recorded in the appropriate eCRF.

The laboratory variables to be measured are presented in the relevant appendix (eg, Appendix A for Arm A).

Additionally, a urine/serum sample will be collected from all women of childbearing potential at screening and before the first dose for a pregnancy test in all combination arms.

If a patient shows an aspartate aminotransferase (AST) **or** alanine aminotransferase (ALT) ≥3× upper limit of normal (ULN) **or** total bilirubin ≥2× ULN, refer to Appendix E for further instructions on cases of increases in liver biochemistry and evaluation of Hy's Law. These cases should be reported as SAEs if, after evaluation, they meet the criteria for a Hy's Law case or if any of the individual liver test parameters fulfil any of the SAE criteria.

Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the eCRF. Situations in which laboratory safety results should be reported as AEs are described in Section 7.3.7.

All patients who have any Common Terminology Criteria 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 Common Terminology Criteria Grade 1 or 2, unless these values are not likely to improve because of the underlying disease.

6.2.2 Physical examination

Physical examinations will be performed according to the assessment schedules (see individual arm appendix). Full physical examinations will include assessments of the head, eyes, ears, nose, and throat and the respiratory, cardiovascular, gastrointestinal, urogenital, musculoskeletal, neurological, dermatological, hematologic/lymphatic, and endocrine systems. Height will be measured at screening only. Targeted physical examinations are to be utilized by the Investigator on the basis of clinical observations and symptomatology. Situations in which physical examination results should be reported as AEs are described in Section 7.3.7.

6.2.3 Resting 12-lead ECG

Resting 12-lead ECGs will be recorded at screening, at the commencement of each treatment cycle for patients in Arms B and C (see Appendix B section 5 and Appendix C.), and as clinically indicated throughout the study (see relevant arm appendix). ECGs should be obtained after the patient has been in a supine position for 5 minutes and recorded while the patient remains in that position.

In case of clinically significant ECG abnormalities, including a heart rate corrected QT interval (Fridericia's formula) (QTcF) value >470 ms or a shift from baseline of ≥ 60ms, 2 additional 12 lead ECGs should be obtained over a brief period (eg, 30 minutes) to confirm the finding.

Situations in which ECG results should be reported as AEs are described in Section 7.3.7.

6.2.4 Vital signs

Semi-supine blood pressure, pulse, temperature, and respiration rate will be measured after 10-minute rest. Assessments will be performed at the visits as shown in the study plan (see the appropriate section of the relevant arm appendix) and below.

Situations in which vital signs results should be reported as AEs are described in Section 7.3.7. For any AEs of infusion reactions, vital signs values should be entered into the case report form (CRF).

6.3 Other assessments

6.3.1 WHO/ECOG performance status

WHO/ECOG performance status will be assessed at the times specified in the assessment schedules (see relevant arm appendix) based on the following:

0. Fully active; able to carry out all usual activities without restrictions.

1. Restricted in strenuous activity, but ambulatory and able to carry out light work or work of a sedentary nature (eg, light housework or office work).

2. Ambulatory and capable of self-care, but unable to carry out any work activities; up and about more than 50% of waking hours.

3. Capable of only limited self-care; confined to bed or chair more than 50% of waking hours.

4. Completely disabled; unable to carry out any self-care and totally confined to bed or chair.

Any significant change from baseline or screening must be reported as an AE.

6.4 Pharmacokinetics

Please refer to the relevant arm appendix for details of PK requirements that are required on an investigational product basis (eg, Appendix A for Arm A).

6.4.1 Collection of samples

Blood samples for determination of study drug in serum will be obtained according to the assessment schedules (see relevant arm appendix).

6.4.2 Determination of drug concentration

Samples for determination of drug concentration in serum will be analyzed by a designated third party on behalf of AstraZeneca using an appropriate bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

6.4.3 Storage and destruction of pharmacokinetic samples

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

PK samples may be disposed of and destroyed or anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled PK samples to further evaluate and validate the analytical method. Results from such analyses may be reported separately from the Clinical Study Report (CSR).

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the CSR but separately in a Bioanalytical Validation Report.

Any residual back-up PK samples may be used for future exploratory biomarker research (in this case, residual back-up PK samples will be shipped to AstraZeneca Biobank; see details in the Laboratory Manual).

6.5 Pharmacodynamics

6.5.1 Collection of samples

Blood (mandatory) and archival tumor samples (if available) for exploratory biomarker analyses will be obtained according to the schedules presented in each arm. Details for collection, volumes, storage, and shipment of biologic samples are presented in a separate Laboratory Manual.

Please see Section 6.6.1.

6.6 Biomarker analysis

By participating in this study, the patient consents to the collection and use of donated biological samples as described here. Samples will be obtained from all screened patients.

Biological samples (eg, archived tumor samples) will be collected and may be analyzed for exploratory biomarkers to assess correlations with disease activity, effects of study drug, clinical outcomes, and toxicity.

Samples will be obtained according to the assessment schedules provided in each arm.

Details for collection, volumes, storage, and shipment of biologic samples are presented in a separate Laboratory Manual.

All samples collected for biomarker analyses will be stored at the study site, a reference laboratory, or at AstraZeneca facilities and may be used for subsequent research relevant to evaluating biological and/or clinical response as described in the exploratory analyses section.

The results may be pooled with biomarker data from other studies to evaluate biological responses across indications and to compare results in monotherapy versus combination settings.

6.6.1 Exploratory biomarkers

The exploratory biomarker plan is described by sample type below.

CCI

CCI .

CCI

CCI

CCI

CCI

CCI

CCI

CCI

6.6.2 Management of biomarker data

The biomarker data will have unknown clinical significance. AstraZeneca will not provide biomarker research results to patients, their family members, any insurance company, an employer, clinical study Investigator, general physician, or any other third party, unless required to do so by law. The patient's samples will not be used for any purpose other than those described in the study protocol.

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

6.6.3 Storage, re-use, and destruction of biological samples

Samples will be stored for a maximum of 15 years from the date of the Last Patient Last Visit, after which they will be destroyed. Summaries and analyses for exploratory biomarkers will be documented in a separate analysis plan and will be reported outside the CSR in a separate report. The results of this biomarker research may be pooled with biomarker data from other studies involving the agents tested in this study to generate hypotheses to be tested in future research.

6.6.4 Labeling and shipment of biological samples

The Principal Investigator ensures that samples are labeled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria); see **Appendix D**, International Airline Transportation Association 6.2 Guidance Document.

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

6.6.5 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The Principal Investigator at each center will keep full traceability of collected biological samples from the patients while in storage at the center until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

The sample receiver will keep full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

AstraZeneca keeps oversight of the entire life cycle through internal procedures, monitoring of study sites, and auditing of external laboratory providers.

Samples retained for further use are registered in the AstraZeneca Biobank during the entire life cycle.

6.6.6 Withdrawal of informed consent for donated biological samples

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

The Principal Investigator will:

- Ensure that AstraZeneca is immediately notified of the patients' withdrawal of informed consent to the use of donated samples
- Ensure that biological samples from that patient, if stored at the study site, are immediately identified, disposed of, or destroyed and the action is documented
- Ensure that the laboratory(ies) holding the samples is/are immediately informed about the withdrawn consent and that samples are disposed of or destroyed, the action is documented, and the signed document is returned to the study site
- Ensure that the patient and AstraZeneca are informed about the sample disposal

7. SAFETY REPORTING AND MEDICAL MANAGEMENT

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

7.1 Definition of adverse events

An AE is the development of an undesirable medical condition (other than progression of the malignancy under evaluation) or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver), or the abnormal results of an investigation (eg, laboratory findings, ECG). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

7.2 Definitions of serious adverse event

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, or follow-up) that fulfils 1 or more of the following criteria:

- Results in death

- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent 1 of the outcomes listed above

For further guidance on the definition of an SAE, see Appendix H.

7.3 Recording of adverse events

7.3.1 Time period for collection of adverse events

AEs and SAEs will be recorded from the time of informed consent, throughout the treatment period, and up to the follow-up period (see relevant arm appendix for number of days after the last dose of study treatment).

7.3.2 Follow-up of unresolved adverse events

During the course of the study, all AEs and SAEs should be proactively followed up for each patient for as long as the event is ongoing. Every effort should be made to obtain a resolution for all events, even if the events continue after the patient has discontinued study drug or the study has completed.

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

7.3.2.1 Post-study events

After the patient has been permanently withdrawn from the study, there is no obligation for the Investigator to actively report information on new AEs or SAEs occurring in former study patients after the arm-designated number of days. However, if an Investigator learns of any SAEs, including death, at any time after the patient has been permanently withdrawn from study, and he or she considers there is a reasonable possibility that the event is related to study treatment, the Investigator should notify AstraZeneca, Patient Safety, or its representative.

7.3.3 Variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date and time when the AE started and stopped
- The maximum Common Terminology Criteria for Adverse Event (CTCAE) grade reported
- Changes in CTCAE grade (report only the maximum CTCAE grade for each calendar day)
- Whether the AE is serious or not
- Investigator causality rating against the study treatment (yes or no)
- Action taken with regard to study treatment
- Administration of treatment for the AE
- Whether AE caused patient's withdrawal from study (yes or no)
- Outcome

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

- Date AE met criteria for SAE
- Date Investigator became aware of the SAE
- Seriousness criteria
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Whether an autopsy was performed
- Causality assessment in relation to study procedure(s)
- Causality assessment in relation to other medication, as explained in Section 7.3.4
- Description of AE

The grading scales found in the revised National Cancer Institute (NCI) CTCAE version 4.03 will be used for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used. A copy of the CTCAE version 4.03 can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity, whereas seriousness is defined by the criteria in Section 7.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE unless it meets the criteria shown in Section 7.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE when it satisfies the criteria shown in Section 7.2.

7.3.4 Causality collection

The Investigator will assess causal relationships between the IP and each AE, and answer "yes" or "no" to the question "Do you consider that there is a reasonable possibility that the event may have been caused by the Investigational Product?"

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

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

7.3.5 Relationship to protocol procedures

The Investigator is also required to provide an assessment of the relationship of SAEs to protocol procedures on the SAE report form. This includes both non-treatment-emergent (ie, SAEs that occur prior to the administration of IP) and treatment-emergent SAEs. A protocol-related SAE may occur as a result of a procedure or intervention required during the study (eg, blood collection). The following guidelines should be used by Investigators to assess the relationship of SAEs to the protocol:

- Protocol related: The event occurred due to a procedure or intervention that was described in the protocol for which there is no alternative etiology present in the patient's medical record.

- Not protocol related: The event is related to an etiology other than the procedure or intervention that was described in the protocol. The alternative etiology must be documented in the study patient's medical record.

7.3.6 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study personnel, "Have you had any health problems since the previous visit/you

were last asked?", or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

7.3.7 Adverse events based on examinations and tests

The results from protocol-mandated laboratory tests and vital signs will be summarized in the CSR. Deterioration as compared to baseline in protocol-mandated laboratory values and vital signs should, therefore, only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible, the reporting Investigator uses the clinical term rather than the laboratory term (eg, anemia versus low hemoglobin value).

In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

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

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

7.3.8 Hy's Law

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

7.3.9 Disease progression

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

7.3.10 New cancers

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

7.3.11 Deaths

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

- Deaths that are clearly the result of disease progression should be reported to the Study Monitor/Physician at the next monitoring visit and should be documented in the eCRF in the Statement of Death page. It should not be reported as an SAE.

- Where death is not due (or not clearly due) to progression of disease under study, the AE causing the death must be reported to the study monitor as an SAE within 24 hours. It should also be documented in the Statement of Death page in the eCRF. The report should contain a comment regarding the co-involvement of PD, if appropriate, and should assign main and contributory causes of death.

- Deaths with an unknown cause should always be reported as an SAE. It should also be documented in the Statement of Death page in the eCRF. A post-mortem maybe helpful in the assessment of the cause of death, and if performed, a copy of the post-mortem results should be forwarded to AstraZeneca Patient Safety or its representative within the usual timeframes.

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

7.4 Reporting of serious adverse events

All SAEs have to be reported whether or not considered causally related to the IP or to the study procedure(s). All SAEs will be recorded in the eCRF and submitted as described in each arm.

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

The designated AstraZeneca representative will work with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within**

1 calendar day of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

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

Please refer to the arm-specific Safety Reporting Guidelines. The AstraZeneca representative will advise the Investigator/study site personnel how to proceed. AstraZeneca or their representative will provide regulatory authorities, Ethics Committees (ECs), and Principal Investigators with clinical safety updates/reports according to local requirements.

The Principal Investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and is to be reported as such.**

7.5 Adverse events of special interest

An adverse event of special interest (AESI) is one of scientific and medical interest specific to the understanding of the study treatment and may require close monitoring and rapid communication by the Investigator to the Sponsor. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of the individual investigational products.

Please see the relevant arm appendix for applicable AESIs.

7.6 Overdose

Use of any agent studied in doses in excess of that specified in the protocol or arms is considered to be an overdose. There is currently no specific treatment in the event of overdose of any of these agents, and possible symptoms of overdose are not established.

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

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

The designated AstraZeneca representative will work with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with an SAE, the standard reporting timelines apply; see Section 7.4. For other overdoses, reporting must occur within 30 days.

7.7 Pregnancy

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

Pregnancy discovered before the study patient has received any study drugs.

7.7.1 Maternal exposure

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

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

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

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 to5 calendar days for SAEs (see Section 7.4) and within 30 days for all other pregnancies.

The same timelines apply when information on the outcome of the pregnancy is available.

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

7.7.2 Paternal exposure

Please see specific arm for the required time for male patients to refrain from fathering a child, donating sperm during the study, or details of reporting outcomes of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose of study medication.

Where a report of pregnancy is received, prior to obtaining information about the pregnancy, the Investigator must obtain the consent of the patient's partner. Therefore, the local study team should adopt the generic informed consent form (ICF) template in line with local procedures and submit it to the relevant ECs/Institutional Review Boards (IRBs) prior to use.

7.8 Management of investigational product-related toxicities

Please refer to the relevant section (eg, Section 7.5 for Arm A) for specific toxicity management guidelines applicable to each arm of the study.

All toxicities will be graded according to NCI CTCAE version 4.03 (see study-specific sub-protocols).

7.9 Study governance and oversight

A Review Committee, which includes the Principal Investigator, the AstraZeneca Study Physician, and statisticians, will convene after the first 10 patients are enrolled onto each arm to assess whether the arm should continue to accrue or stop recruitment based on an interim analysis including ORR (see section 9.5.7). The recommendation of the Review Committee will be discussed at a clinical project level before endorsement.

If the decision is made to open stage 2 of a particular arm the Review Committee will review the results of the primary analysis for the first 20 subjects after completion of 12 weeks follow up. Based on the totality of the data and the benefit-risk assessment the Review Committee may recommend expansion of that arm. The recommendation of the Review Committee will be discussed at a clinical project level before endorsement.

No Steering Committee and/or Scientific Advisory Committee will be used in this study. There is an internal AstraZeneca BALTIC Study Team to oversee the global operational and medical monitoring aspects of the study. The safety of all subjects in the BALTIC study is closely monitored on an ongoing basis by this team in consultation with AstraZeneca Patient Safety and clinical teams responsible for the individual products under investigation in each arm. Issues identified will be addressed; for instance, this could involve amendments to the study protocol and letters to Investigators.

8. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

8.1 Identity of investigational product(s)

Please refer to the relevant appendix (eg, Appendix A for Arm A) for specific IP information applicable to each arm of the study.

8.1.1 Duration of treatment

Unless specific treatment discontinuation criteria are met, all patients will continue therapy until disease progression.

8.1.2 Follow up of patients post discontinuation of study drug

Please refer to the relevant appendix (eg, Appendix A for Arm A) for specific information applicable to each arm of the study.

8.2 Dose and treatment regimens

Please refer to the relevant arm appendix (eg, Appendix A for Arm A) for specific dose and treatment regimens.

8.3 Labeling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 and regulatory requirements of each country participating in the study. The labels will be translated into local languages where applicable as required by local regulations. Labels will be provided as either singlepanel labels or as multi-language booklet labels.

The patient emergency contact details and patients' dosing instructions will not be on the labels but can be found in the informed consent and the "Patient Information Card." For emergency purposes, the patient must be in possession of the emergency contact details at all times.

Please see the relevant arm appendix (eg, Appendix A for Arm A) for specific labeling information.

8.4 Storage

All study medications should be kept in a secure place under appropriate storage conditions. The IP label on the pack/bottle/carton will specify the appropriate storage. Storage is also described in the IB of each product and in the IP Handling Instruction

8.5 Compliance

The administration of all study drugs (including IPs) should be recorded in the appropriate sections of the CRF.

8.6 Accountability

The study drug provided for this study will be used only as directed in the study protocol.

Study site personnel will account for all study drugs received at the site, unused study drugs, and study drugs for appropriate destruction. Certificates of delivery, destruction, and/or return should be signed.

8.7 Concomitant and other treatments

The Investigator must be informed as soon as possible about any medication taken from the time of screening until the end of the clinical treatment phase of the study including the follow-up period following the last dose of treatment. Any concomitant medication(s), including herbal preparations, taken during this time will be recorded in the eCRF.

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

Restricted, prohibited, and permitted concomitant medications are described in the relevant arm appendix.

8.7.1 Other concomitant treatment

Other medication other than that described above, which is considered necessary for the patient's safety and well-being, may be given at the discretion of the Investigator and recorded in the appropriate sections of the CRF.

8.8 Post-study access to study treatment

Patients are permitted to receive study treatment until confirmed progression. AstraZeneca may continue to provide open-label drugs to patient, if such becomes available.

After discontinuation of study treatment, the Investigator will be at liberty to define further most appropriate anti-cancer treatment.

9. STATISTICAL ANALYSES BY ASTRAZENECA

9.1 Statistical considerations

All statistical analyses will be performed by AstraZeneca or its representatives. The analyses will be descriptive, and no inferential analysis will be performed based on statistical tests.

A comprehensive statistical analysis plan (SAP) will be prepared and finalized within 3 months of enrollment of the first patient, and any subsequent amendments will be documented, with final amendments completed prior to reporting of the data.

9.2 Sample size estimate

This study will enroll up to 40 eligible patients in each treatment arm. Stage 1 will initially enroll a minimum of 10 patients; after a minimum of 12 weeks an interim analysis will be performed, which will determine whether recruitment should expand to the second stage (an additional 10 patients for a total of 20 eligible patients) or stop. If the results of the primary ORR from the completed 2nd stage are encouraging the Review Committee could recommend expansion to add up to an additional 20 eligible subjects (for a total of 40 eligible patients), to further explore the findings.

The table below shows the 2-sided exact 95% confidence intervals (CI) for the ORR of a treatment arm at each stage of the study, assuming the observed ORR is CCI% or CCI%:

ORR	**CCI%**	**CCI**
Stage 1 (10 patients)	(CCI%, CCI%)	(CCI%, CCI%)
Stage 2 (20 patients in total)	(CCI%, CCI%)	(CCI%, CCI%)

ORR	[redacted]%	[redacted]%
Expansion (40 patients in total)	([redacted]%, [redacted]%)	([redacted]%, [redacted]%)

9.3 Definitions of analysis sets

Definitions of the analysis sets for each outcome variable are provided in Table 1.

Table 1 Summary of outcome variables and analysis populations

Outcome variable	Population
Efficacy data	
ORR, DoR, DCR, TTR, PFS and OS	Full Analysis Set
Demography	Full Analysis Set
PK data	PK Analysis Set
Safety data	
Exposure	Full Analysis Set
AEs	Full Analysis Set
Laboratory measurements	Full Analysis Set
Vital signs	Full Analysis Set
ECGs	Full Analysis Set

AE Adverse Event; DCR Disease control rate; DoR Duration of response; ECG Electrocardiogram; ORR Objective response rate; OS Overall survival; PFS Progression-free survival; PK Pharmacokinetic; TTR Time to response.

9.3.1 Full Analysis Set

The Full Analysis Set (FAS) will include all treated patients. Patients who were enrolled but did not subsequently go on to receive IP are not included in the FAS.

9.3.2 PK Analysis Set

All patients who received at least 1 dose of study treatment per the protocol for whom any post-dose data are available and who do not violate or deviate from the protocol in ways that would significantly affect the PK analyses will be included in the PK Analysis Set. The population will be defined by the Study Physician, Pharmacokineticist, and Statistician prior to any analyses being performed.

9.4 Outcome measures for analyses

9.4.1 Calculation or derivation of efficacy variables

The analysis of the primary endpoint, ORR, and the analyses of the secondary endpoints, DoR, DCR, TTR, and PFS, will be based on site Investigator assessment using RECIST 1.1. In addition, OS will also be evaluated.

9.4.1.1 RECIST 1.1-based endpoints

Investigator RECIST 1.1-based assessments

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

At each visit, patients will be programmatically assigned a RECIST 1.1 visit response of CR, PR, SD, or PD depending on the status of their disease compared with baseline and previous assessments. Baseline will be assessed within the 28 days prior to enrollment. If a patient has had a tumor assessment that cannot be evaluated, then the patient will be assigned a visit response of NE (unless there is evidence of progression, in which case the response will be assigned as PD).

Please refer to Appendix F for the definitions of CR, PR, SD, and PD.

9.4.1.2 Primary endpoint (objective response rate)

ORR (per RECIST 1.1 as assessed by the site Investigator) is defined as the number (%) of patients with a confirmed objective response of CR or PR and will be based on patients in the evaluable set.

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. Therefore, data obtained up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of ORR. Any patient who discontinues treatment without progression, receives a subsequent therapy, and then responds will not be included as responders in the ORR.

For sensitivity analysis, ORR may be assessed using the RECIST 1.1 site Investigator tumor data following a modification where any objective progression requires confirmation. Therefore, data obtained up until confirmed progression, or the last evaluable assessment in the absence of a confirmed progression, may be included in the assessment of ORR. Note that the response may be after an unconfirmed progression.

9.4.1.3 Secondary endpoints

Secondary efficacy variables include DoR, DCR, TTR, PFS, and OS. Efficacy data will be summarized and analyzed based on the FAS.

Duration of response

DoR (per RECIST 1.1 as assessed by the site Investigator) will be defined as the time from the date of first documented response (which is subsequently confirmed) until the first date of documented progression or death in the absence of disease progression. The end of response should coincide with the date of progression or death from any cause used for the RECIST 1.1 PFS endpoint.

The time of the initial response will be defined as the latest of the dates contributing toward the first visit response of CR or PR. If a patient does not progress following a response, then their DoR will be censored at the PFS censoring time. DoR will not be defined for those patients who do not have documented response (which is subsequently confirmed).

Sensitivity analyses of DoR may be performed based on Investigator assessment according to RECIST 1.1 modified for confirmation of progression.

Disease control rate

DCR at 12 weeks is defined as the percentage of patients who have a best objective response of CR or PR in the first 13 weeks (to allow for a late assessment within the assessment window) or who have demonstrated SD for a minimum interval of 11 weeks (to allow for an early assessment within the assessment window) following the start of study treatment.

DCR will be determined programmatically based on RECIST 1.1 using site Investigator data and all data up until the first progression event.

Sensitivity analyses of DCR may be performed based on Investigator assessment according to RECIST 1.1 modified for confirmation of progression.

Time to response

TTR (per RECIST 1.1 as assessed by the Investigator) is defined as the time from the date of first dose until the first date of documented response (which is subsequently confirmed). The date of first documented response should coincide with that used for the RECIST 1.1 DoR endpoint. TTR will not be defined for those patients who do not have documented response (which is subsequently confirmed).

Progression-free survival

PFS (per RECIST 1.1 as assessed by the site Investigator) will be defined as the time from the date of first dose until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from therapy or receives another anticancer therapy prior to progression.

Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST 1.1 assessment. However, if the patient progresses or dies after 2 or more missed visits, the patient will be censored at the

time of the latest evaluable RECIST 1.1 assessment. If the patient has no evaluable visits or does not have baseline data, they will be censored at Day 1 unless they die within 2 visits of baseline.

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

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

- Date of progression will be determined based on the earliest of the dates of the component that triggered the progression on the first set of scans that indicates progression.

- When censoring a patient for PFS, the patient will be censored at the latest of the dates contributing to a particular overall visit assessment.

Sensitivity analyses of PFS may be performed based on Investigator assessment according to RECIST 1.1 modified for confirmation of progression.

Overall survival

OS is defined as the time from the date of first dose until death due to any cause. Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive.

Note: Survival calls will be made in the week following the date of data cut-off for the analysis, and if patients are confirmed to be alive or if the death date is post the data cut-off date, these patients will be censored at the date of data cut-off. Death dates may be found by checking publicly available death registries.

9.4.2 Calculation or derivation of safety variables

9.4.2.1 Adverse events

Safety and tolerability will be assessed in terms of AEs (including SAEs), deaths, laboratory data, vital signs, ECGs, and exposure. These will be collected for all patients. Data from all cycles of treatment will be combined in the presentation of safety data. "On treatment" will be defined as assessments between date of start dose and the time period specified in each specific study arm following discontinuation of IP (please see relevant arm appendix for assessment time periods). For AEs, on treatment (or treatment-emergent AEs) will be defined as any AEs that started after dosing or prior to dosing and that worsens following exposure to the treatment.

AEs observed for the time period specified in each specific study arm following discontinuation of study treatment or until the initiation of the first subsequent therapy following discontinuation of treatment (whichever occurs first) will be used for the reporting of the AE summary tables. This will more accurately depict AEs attributable to study

treatment only, as a number of AEs up to the time period specified in each specific study arm following discontinuation of the study agents are likely to be attributable to subsequent therapy. However, to assess the longer term toxicity profile, AE summaries will also be produced containing AEs observed up until the time period specified in each specific study arm following discontinuation of the study agents (ie, without taking subsequent therapy into account). Any events in this period that occur after a patient has received further therapy for cancer (following discontinuation of study treatment) will be flagged in the data listings.

A separate data listing of AEs occurring more than until the time period specified in each specific study arm after discontinuation of IP will be produced. These events will not be included in AE summaries.

9.4.2.2 Safety assessments

For the change from baseline summaries for vital signs, laboratory data, ECGs, and physical examination, the baseline value will be the latest result obtained prior to the start of study treatment.

The QTcF will be derived during creation of the reporting database using the reported ECG values (RR and QT).

QTcF=QT/RR^ (1/3) where RR is in seconds

Corrected calcium will be derived during creation of the reporting database using the following formulas:

Corrected calcium (mmol/L)=Total calcium (mmol/L)+([40-albumin (G/L)]×0.02).

The denominator used in laboratory summaries will only include evaluable patients, in other words, those who had sufficient data to have the possibility of an abnormality.

For example:

- If a CTCAE criterion involves a change from baseline, evaluable patients would have both a pre-dose and at least 1 post-dose value recorded.
- If a CTCAE criterion does not consider changes from baseline, to be evaluable, the patient need only have 1 post dose-value recorded.

The denominator in vital signs data should include only those patients with recorded data.

9.4.3 Calculation or derivation of patient-reported outcome variables

Not applicable.

9.4.4 Calculation or derivation of pharmacokinetic variables

9.4.4.1 Population pharmacokinetics and exposure-response/safety analysis

No population pharmacokinetics and exposure-response/safety analysis is planned for this study given the small number of patients in each arm. However the PK, pharmacodynamics, demographic, safety, and efficacy data collected in this study may also be combined with similar data from other studies and explored using population PK and/or PK-pharmacodynamic methods. See the individual arm sub-protocol appendix (e.g. Appendix A for Arm A) for details of the PK analysis planned in that arm.

9.4.4.2 Pharmacokinetic analysis

PK concentration data and summary statistics will be tabulated. Individual and mean blood concentration time profiles will be generated. PK parameters will be determined using standard non-compartmental methods. The following PK parameters will be determined after the first and steady-state doses: peak and trough concentration (as data allow). Samples below the lower limit of quantification will be treated as missing in the analyses.

9.4.5 CCI

CCI

9.4.6 Calculation or derivation of pharmacogenetic variables

Not applicable.

9.5 Methods for statistical analyses

Descriptive statistics will be used for all variables, as appropriate, and will be presented by treatment arm. Continuous variables will be summarized by the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by frequency counts and percentages for each category. Unless otherwise stated, percentages will be calculated out of the population total for the corresponding treatment arm.

Baseline will be the last assessment of the variable under consideration prior to the intake of the first dose of IP, except for efficacy variables. For efficacy variables, baseline is defined as the last visit prior to first dose of study treatment.

All data collected will be listed. Efficacy and safety data will be summarized and analyzed based on the FAS. As a sensitivity analysis, efficacy data may also be summarized/analyzed in a subgroup of FAS for patients without important protocol deviations. PK data will be summarized and analyzed based on the PK Analysis Set.

If the results of final ORR from the completed 2nd stage of any arm are encouraging the Review Committee could recommend expansion to add up to an additional 20 eligible subjects

into that arm to further explore the findings (for a total of 40 eligible patients). Refer to Section 9.5.8 for information on the statistical analysis performed for the expansion cohort.

9.5.1 Primary analysis

The primary analysis of ORR will occur approximately 12 weeks after the last patient has initiated treatment. This is planned to ensure the data cut off for ORR analysis follows the 12 week RECIST assessment for the last subject to be treated. However, in the situation where this scan does not occur due to this subject having experienced another progression event (e.g. death) the primary analysis DCO will be when all subjects have been followed for at least 12 weeks or until death if this is earlier. All study endpoints will be analyzed at this time including OS. The Sponsor will determine at that time whether any further follow up for OS would be required.

If the decision is made to close the Arm at the interim analysis the Sponsor will determine the appropriate length of follow up to ensure sufficient data collection for the primary analysis in that Arm.

9.5.2 Analysis of the primary variable(s)

For the primary endpoint, ORR will be estimated with 95% exact CIs separately for each treatment arm. The primary analysis will be based on the programmatically derived ORR based on RECIST 1.1 based on site Investigator assessments, and using all scans regardless of whether they were scheduled or not. A sensitivity analysis will be performed on programmatically derived ORR (RECIST 1.1 modified for confirmation of progression) to determine if there is any difference when using progression confirmation rules. The primary analysis population for ORR will be the FAS.

Summaries will be produced that present the number and percentage of patients with a tumor response (CR/PR). The number (%) of patients with a confirmed response and the number (%) of patients with a single visit response (ie, an unconfirmed response) will also be presented.

9.5.3 Analysis of the secondary variable(s)

9.5.3.1 Duration of response

Kaplan-Meier plots of DoR based on the site Investigator assessment of RECIST 1.1 will be presented for each treatment arm if appropriate. Median DoR will also be summarized. Only patients who have a confirmed response will be included in this summary table.

9.5.3.2 Disease control rate

The DCR based on the site Investigator assessment of RECIST 1.1 will be summarized (ie, number of patients [%] for each treatment arm at 3 months).

9.5.3.3 Time to response

The TTR based on the site Investigator assessment of RECIST 1.1 will be summarized (ie, number of patients [%] based on the number of responders for each treatment arm) by the scheduled assessment timepoint that the response was first observed. Additionally, descriptive summary statistics (ie, minimum, maximum, median, Q1, and Q3) will also be presented. Only patients who have a confirmed response will be included in this summary table.

9.5.3.4 Progression-free survival

Kaplan-Meier plots of PFS will be presented for each treatment arm. Summaries of the number and percentage of patients experiencing a PFS event, and the type of event (RECIST 1.1 or death) will be provided along with median PFS for each treatment.

9.5.3.5 Overall survival

Kaplan-Meier plots will be presented by treatment arm. Summaries of the number and percentage of patients who have died, those still in survival follow-up, those lost to follow-up, and those who have withdrawn consent will be provided along with the median OS for each treatment arm.

9.5.4 Safety data

Safety and tolerability data will be presented separately for each treatment arm using the FAS.

Data from all cycles will be combined in the presentation of safety data. AEs (both in terms of Medical Dictionary for Regulatory Activities [MedDRA] preferred terms and CTCAE grade) will be listed individually by patient. The number of patients experiencing each AE will be summarized by CTCAE grade. Additionally, data presentations of the rate of AEs per person-years at risk may be produced.

Other safety data will be assessed in terms of physical examination, clinical chemistry, hematology, vital signs, and ECGs. Exposure to IP will be summarized. Time on study, IP dose delays/interruptions, and dose reductions will also be summarized. At the end of the study, appropriate summaries of all safety data will be produced as defined in the SAP.

9.5.5 Pharmacokinetic data

PK concentration data will be listed for each patient and each dosing day (where data allow), and a summary will be provided for all evaluable patients in the PK Analysis Set.

9.5.6 CCI

CCI

CCI

CCI [redacted]

9.5.7 Interim analysis

An interim analysis will be conducted on each arm. This will assess ORR in all evaluable patients in that arm, to determine whether to progress to stage 2 of the arm. The DCO for the interim analysis will take place approximately 12 weeks after the 10th patient has initiated treatment. If there are CCI responders, then there is a low posterior probability of achieving ORR of at least CCI% in 20 patients and the Review Committee may decide that no further patients will be recruited to the arm. If there are CCI responders out of 10, then an additional 10 patients will be recruited and the final estimate of ORR will be based on 20 patients. If there arCCI r more responders out of 10 patients, then it will be regarded as strong efficacy and the Review Committee may decide to stop recruitment into the particular arm.

The posterior probability of having at leasCCI responders in 20 patients for CCI responders in 10 patients is shown below.

	CCI	CCI	CCI	CCI
CCI	CCI %	CCI %	CCI %	CCI %

9.5.8 Analysis following expansion

If the Review Committee decides to recommend expansion of any given arm (for a maximum total of 40 eligible patients), no further interim analysis will be conducted and the entire expansion cohort (additional 20 patients) will be recruited with no break. Primary analysis will be ORR of all subjects recruited to the individual arm (i.e. 1st and 2nd stage cohorts plus the expansion cohort) after 12 weeks follow up of the last patient dosed in that arm. However, a sensitivity analysis may be performed to analyze the cohorts separately due to potential changes in population (e.g. due to differences in the 1st line therapy) between recruitment of the initial 2 cohorts and the expansion cohort of that arm.

10. STUDY AND DATA MANAGEMENT BY ASTRAZENECA

10.1 Training of study site personnel

Before the first patient is entered into the study, an AstraZeneca representative or delegate will review and discuss the requirements of the CSP and related documents with the investigational staff and also train them in any study-specific procedures (including those listed in the Laboratory Manual) and the Electronic Data Capture (EDC(s)) used.

The additional requirements for the collection of the patients' samples for the biomarker research will also be made clear.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing, and other staff).

10.2 Monitoring of the study

During the study, an AstraZeneca representative will have regular contacts with the study site, including visits to:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the CRFs, that biological samples are handled in accordance with the Laboratory Manual, and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (eg, clinic charts).
- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported, and biological samples are identified and disposed of/destroyed accordingly, and the action is documented and reported to the patient.

The AstraZeneca representative will be available between visits if the Investigator(s) or other staff at the center needs information and advice about the study conduct.

10.2.1 Source data

Refer to the Clinical Study Agreement for location of source data.

The Head of the study site and the Principal Investigator/Investigator will cooperate for monitoring and audit by AstraZeneca and accept inspection by the IRB or regulatory authorities. All study documents such as raw data will be open for direct access to source data at the request of the monitor and the auditor of AstraZeneca, the IRB, or regulatory authorities.

The monitor will verify data from the eCRFs against source data before the Principal Investigator signs the eCRFs to ensure accuracy and completeness of documentation and to ensure that the Principal Investigator has submitted the eCRFs to AstraZeneca.

10.2.2 Study agreements

The Principal Investigator at each center should comply with all the terms, conditions, and obligations of the Clinical Study Agreement or equivalent for this study. In the event of any inconsistency between this CSP and the Clinical Study Agreement, the terms of the CSP shall prevail with respect to the conduct of the study and the treatment of patients, and in all other respects, not relating to study conduct or treatment of patients, the terms of the Clinical Study Agreement shall prevail.

Specific reference to requirements relating to the biomarker research will be included in the study agreement(s).

Agreements between AstraZeneca and the Principal Investigator should be in place before any study-related procedures can take place or before patients are enrolled.

10.2.3 Archiving of study documents

The Investigator follows the principles outlined in the Clinical Study Agreement.

10.3 Study timetable and end of study

The end of the study is defined as "the last visit of the last patient undergoing the study." The study is expected to start in Q3 2016 and to end by Q1 2021.

The study may be terminated at individual centers if the study procedures are not being performed according to Good Clinical Practice (GCP) or if recruitment is too slow. AstraZeneca may also terminate the entire study or individual sub-studies prematurely if concerns for safety arise within this study or in any other study with agents used in any of the sub-study arms.

10.4 Data management by AstraZeneca

Data management will be performed by a chosen vendor according to the Data Management Plan. AEs and medical/surgical history will be classified according to the terminology of the latest version of the MedDRA. Medications will be classified according to the AstraZeneca Drug Dictionary. All coding will be performed by the Medical Coding Team at the AstraZeneca Data Management Center.

The data collected through third-party sources will be obtained and reconciled against study data.

Data queries will be raised for inconsistent, impossible, or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The Data Management Plan will also clarify the roles and

responsibilities of the various functions and personnel involved in the data management process.

When all data have been coded, validated, signed, and locked for a specific arm, a clean file will be declared and the final database will be locked for that arm.

Serious adverse event reconciliation

SAE reconciliation reports are produced and reconciled with the Patient Safety database and/or the investigational site.

Data management of genotype data

Not applicable.

Data associated with human biological samples

Data associated with biological samples will be transferred from laboratory(ies) internal or external to AstraZeneca.

11. ETHICAL AND REGULATORY REQUIREMENTS

11.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonization (ICH)/GCP, applicable regulatory requirements, and the AstraZeneca policy on Bioethics and Human Biological Samples.

11.2 Patient data protection

The ICF will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

AstraZeneca will not provide individual genotype results to patients, any insurance company, any employer, their family members, general physician, or any other third party, unless required to do so by law**.**

11.3 Ethics and regulatory review

An EC or IRB should approve the final study protocol, including the final version of the ICF and any other written information and/or materials to be provided to the patients. The Investigator will ensure the distribution of these documents to the applicable EC or IRB and to the study site staff.

The opinion of the EC or IRB should be given in writing. The Investigator should submit the written approval to AstraZeneca before enrollment of any patient into the study.

The EC or IRB should approve all advertising used to recruit patients for the study.

AstraZeneca should approve any modifications to the ICF that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the EC or IRB annually.

Before enrollment of any patient into any arm of the study, the final study protocol for that arm of the study, including the final version of the ICF, should be approved by the national regulatory authority or a notification to the national regulatory authority should be provided, according to local regulations.

AstraZeneca will handle the distribution of these documents to the national regulatory authorities.

AstraZeneca will provide regulatory authorities, ECs or IRBs, and Principal Investigators safety updates or reports according to local requirements.

Each Principal Investigator is responsible for providing the EC or IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the IP. AstraZeneca will provide this information to the Principal Investigator so that he or she can meet these reporting requirements.

11.4 Informed consent

The Principal Investigator(s) at each center will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, and possible risk and benefit of the study
- Ensure each patient is notified that they are free to discontinue from the study at any time
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original signed ICF(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed ICF is given to the patient
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the ICF that is approved by an EC or IRB

11.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the Principal Investigator and AstraZeneca.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and, where required, in a new version of the study protocol (revised CSP).

The amendment is to be approved by the relevant EC or IRB and, if applicable, the national regulatory authority, before implementation. Local requirements are to be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator. For distribution to EC or IRB, see Section 11.3.

If a protocol amendment requires a change to a center's ICF, AstraZeneca and the center's EC or IRB are to approve the revised ICF before the revised form is used.

If required by local regulations, any administrative change will be communicated to or approved by each EC or IRB.

11.6 Audits and inspections

Authorized representatives of AstraZeneca, a regulatory authority, or an EC or IRB may perform audits or inspections at the center, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and to determine if data were recorded, analyzed, and accurately reported according to the protocol, GCPs, ICH guidelines, and any applicable regulatory requirements. The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the center.

APPENDIX A ARM A: DURVALUMAB (MEDI4736) + TREMELIMUMAB SUB-PROTOCOL

1. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
anti-HBc	Anti-Hepatitis B core
AST	Aspartate aminotransferase
AUC	Area under the plasma drug concentration-time curve
AUC_{ss}	Area under the plasma drug concentration-time curve at steady state
B7-H1	B7 homolog 1
BP	Blood pressure
C	Cycle
CD	Cluster of differentiation
CL	Clearance
$C_{max,ss}$	Maximum plasma concentration at steady state
CR	Complete response
CRF	Case report form (electronic/paper)
CSR	Clinical Study Report
CT	Computed tomography
CCI	[redacted]
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte-associated antigen 4
$C_{trough,ss}$	Median trough concentration at steady state
DCR	Disease control rate
DNA	Deoxyribonucleic acid
DoR	Duration of response

Abbreviation or special term	Explanation
Durva	Durvalumab (MEDI4736)
ECG	Electrocardiogram
eCRF	Electronic case report form
EGFR	Epidermal growth factor receptor
ECOG	Eastern Cooperative Oncology Group
ED-SCLC	Extensive stage small-cell lung cancer
EOT	End of treatment
EU	Endotoxin unit
FDA	Food and Drug Administration
HBsAg	Hepatitis B virus surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HPV+	Human papilloma virus-positive
IB	Investigator's Brochure
IHC	Immunohistochemistry
IFN	Interferon
International Coordinating Investigator	If a study is conducted in several countries the International Coordinating Investigator is the Investigator coordinating the Investigators and/or activities internationally.
IP	Investigational product
imAE	Immune-mediated adverse event
irAE	Immune-related adverse event
IV	Intravenous
LFT	Liver function test
mAb	Monoclonal antibody
ORR	Overall response rate
OS	Overall survival
NCI	National Cancer Institute
NSCLC	Non-small-cell lung cancer
PD	Progressive disease
PD-1	Programmed cell death 1

Abbreviation or special term	Explanation
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PR	Partial response
q2w	Every 2 weeks
q3w	Every 3 weeks
q4w	Every 4 weeks
q8w	Every 8 weeks
q12w	Every 12 weeks
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
RNA	Ribonucleic acid
SAE	Serious adverse event
SCLC	Smallcell- lung cancer
SD	Stable disease
sPD-L1	Soluble programmed death ligand-1
STS	Softtissue- sarcoma
T_3	Triiodothyronine
T_4	Thyroxine
TB	Tuberculosis
TNBC	Triple Negative Breast Cancer
TKI	Tyrosine kinase inhibitor
TNF	Tumor necrosis factor
Treme	Tremelimumab
TSH	Thyroid stimulating hormone
TTR	Time to response
ULN	Upper limit of normal
USP	United States Pharmacopeia
US	United States
WHO	World Health Organization
w/v	Weight/volume

2. INTRODUCTION

2.1 Background and rationale for conducting this study

Study D419QC00002 is an open-label, multi-center, multi-arm, Phase II study in patients with extensive-stage small cell lung cancer (ED-SCLC) who have refractory or resistant disease, defined as patients who progress during first-line chemotherapy or those who progress within 90 days after completing first-line chemotherapy. Study D419QC00002 is modular in design, allowing evaluation of the safety, tolerability, pharmacokinetics (PK), and anti-tumor activity of different combinations of novel anticancer agents in patients with refractory or resistant ED-SCLC and will consist of a number of study arms, each evaluating the safety and tolerability of a specific combination.

Arm A in Study D419QC00002 investigates the efficacy, safety, and tolerability of intravenous (IV) treatment with durvalumab (MEDI4736) in combination with tremelimumab followed by durvalumab monotherapy until disease progression in patients with ED-SCLC.

It is increasingly understood that cancers are recognized by the immune system, and, under some circumstances, the immune system may control or even eliminate tumors (Du Bois et al 2003, Dunn et al 2004).

Programmed cell death ligand 1 (PD-L1) [B7 homolog 1 (B7-H1), cluster of differentiation (CD) 274] is part of a complex system of receptors and ligands that is involved in controlling T-cell activation. In normal tissue, PD-L1 is expressed on T-cells, B lymphocytes (B-cells), dendritic cells, macrophages, mesenchymal stem cells, bone marrow-derived mast cells, as well as various non-hematopoietic cells (Keir et al 2008). The normal function of PD-L1 is to regulate the balance between T-cell activation and tolerance through interaction with 2 receptors, programmed cell death 1 (PD-1, CD279) and CD80 (B7-1). PD-L1 is also expressed by tumors and acts at multiple sites to help tumors evade detection and elimination by the host immune system. Interactions between the receptors and ligands result in reduced T-cell activation and fewer activated T-cells in the circulation. In the tumor microenvironment, PDL1 expressed on tumor cells binds to PD-1 on activated T-cells reaching the tumor and this delivers an inhibitory signal to those T-cells, preventing them from killing the target tumor cells, and thus protecting the tumor from immune elimination (Zou and Chen 2008).

PD-L1 is expressed in a broad range of cancers with a high frequency of up to 88% in some types of cancer. In a number of these cancers, including lung (Mu et al 2011), renal (Krambeck et al 2007, Thompson et al 2005, Thompson et al 2006), pancreatic (Loos et al 2008, Nomi et al 2007, Wang et al 2010), and ovarian cancers (Hamanishi et al 2007), the expression of PD-L1 is associated with reduced survival and an unfavorable prognosis. In ovarian cancer, for example, the 5-year survival rate in patients with low levels of PD-L1 was 80.2% compared with 52.6% in patients with high levels of PD-L1 (Hamanishi et al 2007). In lung cancer, only 20% of patients with tumors expressing PD-L1 survived for more than 3 years compared with 49% of patients with tumors lacking PD-L1 (Mu et al 2011).

The levels of tumor-infiltrating cells, and more specifically cytotoxic T-cells, have been correlated to improved prognosis in a number of cancers including colorectal, melanoma, and lung cancers (Pages et al 2010), suggesting that an anti-tumor immune response is beneficial to patients.

Binding of cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) to its target ligands (CD80 and CD86) provides a negative regulatory signal, which limits T-cell activation. Anti-CTLA-4 inhibitors antagonize the binding of CTLA-4 to CD80/86 ligands and enhance human T-cell activation as demonstrated by increased cytokine (interleukin-2 and interferon [IFN] gamma) production in vitro in whole blood or peripheral blood mononuclear cell cultures (Tarhini and Kirkwood 2008). In addition, blockade of CTLA-4 binding to CD80/86 by anti-CTLA-4 antibodies results in markedly enhanced T-cell activation and antitumor activity in animal models, including killing of established murine solid tumors and induction of protective antitumor immunity. Therefore, it is expected that treatment with an anti-CTLA-4 antibody will lead to increased activation of the human immune system, increasing antitumor activity in patients with solid tumors.

Pre-clinical data has now been added to with a wealth of clinical data showing that blockade of negative regulatory signals to T-cells such as CTLA-4 and PD-L1 has promising clinical activity. Ipilimumab (YERVOY®) was granted United States (US) Food and Drug Administration (FDA) approval for the treatment of metastatic melanoma and is currently under investigation for several other malignancies whilst nivolumab (OPDIVOR®) and pembrolizumab (KEYTRUDA®), two anti-PD-1 agents, were granted US FDA and European Medicines Agency approval for the treatment of a number of malignancies including metastatic melanoma and squamous and non-squamous cell non-small-cell lung cancer (NSCLC). In addition there is data from agents in the anti-PD-1/PD-L1 class showing clinical activity in a wide range of tumor types.

2.2 Durvalumab (MEDI4736)

Durvalumab is a human monoclonal antibody (mAb) of the immunoglobulin G (IgG) 1 kappa subclass that blocks the interaction of PD-L1 (but not programmed cell death ligand-2) with PD-1 on T cells and CD80 (B7.1) on immune cells (IC). It is being developed by AstraZeneca/MedImmune for use in the treatment of cancer (MedImmune is a wholly owned subsidiary of AstraZeneca; AstraZeneca/MedImmune will be referred to as AstraZeneca throughout this document.) The proposed mechanism of action (MOA) for durvalumab is interference in the interaction of PD L1 with PD 1 and CD80 (B7.1). Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the inhibition of immune responses, including those that may result in tumor elimination. In vitro studies demonstrate that durvalumab antagonizes the inhibitory effect of PD-L1 on primary human T cells resulting in the restored proliferation of IFN-γ (Stewart et al 2015). In vivo studies have shown that durvalumab inhibits tumor growth in xenograft models via a T cell dependent mechanism (Stewart et al 2015). Based on these data, durvalumab is expected to stimulate the patient's antitumor immune response by binding to PD L1 and shifting the balance toward an antitumor response. Durvalumab has been engineered to reduce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity.

To date, durvalumab has been given to more than 6000 patients as part of ongoing studies either as monotherapy or in combination with other anticancer agents. Details on the safety profile of durvalumab monotherapy are summarized in sections 2.6.5 and 2.7.1.1. Refer to the current durvalumab Investigator's Brochure (IB) for a complete summary of non-clinical and clinical information including safety, efficacy and PK.

2.3 Tremelimumab

Tremelimumab is a human immunoglobulin (Ig)G2 mAb that is directed against CTLA-4; cluster of differentiation [CD]152), a cell surface receptor that is expressed primarily on activated T cells and acts to inhibit their activation. Tremelimumab completely blocks the interaction of human CTLA-4 with CD80 and CD86, resulting in increased release of cytokines (interleukin [IL]-2 and interferon [IFN]-γ) from human T cells, peripheral blood mononuclear cells and whole blood (Tarhini and Kirkwood 2008).Tremilimumab is being developed by AstraZeneca for use in the treatment of cancer.

To date, tremelimumab has been given to more than 1500 patients, either as monotherapy or in combination with other anticancer agents. Details on the safety profile are summarized in section 2.7.2.2. Refer to the current tremelimumab IB for a complete summary of non-clinical and clinical information including safety, efficacy and PK.

In cancer immunotherapy, agents that have limited therapeutic effects as single agents can be powerful when combined. Combining immunotherapy agents has been shown to result in improved response rates relative to those in monotherapy. Furthermore, responses appeared to be rapid, deep, and durable (Wolchok et al 2013).

2.4 Durvalumab in combination with tremelimumab

Targeting both PD-1 and CTLA-4 pathways may have an additive or synergistic activity (Pardoll 2012) because the mechanisms of action of CTLA-4 and PD-1 are nonredundant. Recent results from clinical studies evaluating the efficacy of nivolumab (PD-1 inhibitor) and ipilimumab- (CTLA-4 inhibitor) in untreated melanoma patients have shown significant improvement in survival with this combination, which is especially more pronounced in patients who have PD-L1 negative tumors (Larkin et al 2015, Postow et al 2015).

AstraZeneca is also investigating the use of durvalumab + tremelimumab combination therapy for the treatment of cancer.

The development of durvalumab in combination with tremelimumab was initiated in Study D4190C00006 (in NSCLC; hereafter referred to as Study 6) and Study D4190C00010 (in a range of tumor types, including smallcell lung cancer (SCLC); hereafter referred to as Study 10). Preliminary data from these studies suggested this combination improves clinical outcomes in patients with advanced cancer. Based on promising early efficacy and safety data from these studies, further exploration of the benefit-risk of the durvalumab and tremelimumab combination in SCLC is warranted.

To date, more than 1000 patients have received the combination using a number of doses and dosing schedules. Details on the safety profile of durvalumab + tremelimumab combination therapy are summarized in section 2.7.1.2. Refer to the current editions of the durvalumab and tremelimumab IBs for a complete summary of non-clinical and clinical information including safety, PK and efficacy.

2.5 Rationale for study design, doses, and control groups

The rationale for conducting this study is in Section 2.2 of the master protocol.

The rationale for the unmet medical need in refractory or resistant ED-SCLC is described in Section 2.2.1 of the master protocol. The rationale for the specific study design aspects of Arm A is described below.

2.5.1 Rationale for opening expansion cohort

A total of 21 platinum refractory or resistant ED-SCLC patients have received durvalumab 1500 mg + tremelimumab 75 mg via IV infusion q4w, for up to a total of 4 doses/cycles, followed by durvalumab monotherapy 1500 mg IV infusion q4w until PD in stages 1 and 2 of the present study (D419QC00002). CCI [redacted]

CCI [redacted], therefore the data did not support moving directly to a Phase III study. CCI [redacted]

Based on the initial review of the survival data the Review Committee recommended to open an expansion cohort (an additional 20 patients, for a total of 40 eligible patients), to further explore the findings. This recommendation was endorsed by the Clinical Project Team.

2.6 Durvalumab and tremelimumab dose and treatment regimen justification

2.6.1 Durvalumab + tremelimumab combination therapy dose rationale

The durvalumab + tremelimumab combination therapy doses and regimen selected for this study are based on the goal of selecting an optimal combination dose of durvalumab and

tremelimumab that would yield sustained target suppression (soluble programmed death ligand-1 [sPD-L1]), demonstrate promising efficacy, and have an acceptable safety profile.

Patients enrolled in Arm A will receive:

Durvalumab 1500 mg + tremelimumab 75 mg via IV infusion every 4 weeks (q4w), starting on Week 0, for up to a total of 4 doses/cycles followed by durvalumab monotherapy 1500 mg via IV infusion q4w, starting after completion of the 4th cycle of combination treatment, until progressive disease (PD) and Investigator confirmation that the patient is no longer receiving clinical benefit from the treatment. If a patient's weight falls to 30 kg or below (≤30 kg), then the patient should receive weight-based dosing after discussion between Investigator and Study Physician, until the weight improves to > 30 kg, at which point the patient should start receiving the fixed dosing of durvalumab 1500 mg Q4W and 75mg tremelimumab Q4W (during the combination phase of treatment). The equivalent weight based doses to the fixed doses are 20 mg/kg of durvalumab and 1mg/kg tremelimumab Q4W.

2.6.2 Durvalumab + tremelimumab combination therapy pharmacokinetics/Pharmacodynamics data

As of 28 February 2017, a total of 379 patients with advanced NSCLC have been treated in Study D4190C00006. Various dose combinations were explored, with doses of tremelimumab ranging from CCI mg/kg and doses of durvalumab ranging from CCI mg/kg.

An approximately dose-proportional increase in PK exposure (maximum plasma concentration and area under the plasma drug concentration-time curve from time 0 to Day 28) of both durvalumab and tremelimumab was observed over the dose range of CCI mg/kg durvalumab q4w and CCI mg/kg tremelimumab q4w. Exposures following multiple doses demonstrated accumulation consistent with PK parameters estimated from the first dose. The observed PK exposures of durvalumab and tremelimumab following combination were consistent with respective monotherapy data, indicating no PK interaction between these 2 agents.

CCI patients were ADA positive for anti-durvalumab antibodies post-treatment. CCI patients was ADA positive for anti-tremelimumab antibodies post-treatment. No clear relationship between ADA and the dose of either durvalumab or tremelimumab was observed. No obvious association between ADA and safety or efficacy was observed.

Target engagement for durvalumab was assessed using suppression of free sPD-L1 in serum. Following treatment with the durvalumab and tremelimumab combination, complete sPD-L1 suppression (surrogate for PD-L1 targeting) was observed in almost all patients over the dose range of CCI mg/kg durvalumab q4w or q2w. No clear dose-dependent changes in sPD-L1 were identified over the dose range of CCI mg/kg durvalumab q4w or q2w.

Monotonic increases in pharmacodynamic activity were observed with increasing doses of tremelimumab relative to the activity observed in patients treated with durvalumab monotherapy.

There was evidence of augmented pharmacodynamic activity relative to durvalumab monotherapy with combination doses containing [redacted] mg/kg tremelimumab, including both the [redacted] mg/kg durvalumab plus [redacted] mg/kg tremelimumab combinations.

2.6.3 Clinical data

2.6.3.1 Study D4190C00006

In Study D4190C00006 various dose combinations have been explored, with doses of tremelimumab ranging from [redacted] mg/kg and doses of durvalumab ranging from [redacted] mg/kg. Tremelimumab was given on a q4w schedule while durvalumab was explored in both a q4w and q2w schedule, with the goal of identifying the dose combination that best optimizes the risk:benefit profile in an acceptable range of PK and pharmacodynamic values.

Patients treated with doses of tremelimumab above [redacted] mg/kg had a [redacted] rate of adverse events (AEs), including discontinuations due to AEs, serious adverse events (SAEs), and severe AEs. Between the [redacted] mg/kg durvalumab + [redacted] mg/kg tremelimumab and [redacted] mg/kg durvalumab + [redacted] mg/kg tremelimumab cohorts treated at the q2w schedule, the number of patients reporting any AE, ≥ Grade 3 AEs, SAEs, and treatment-related AEs was [redacted] in the [redacted] mg/kg durvalumab + [redacted] mg/kg tremelimumab cohort than the [redacted] mg/kg durvalumab + [redacted] mg/kg tremelimumab cohort. A similar pattern was noted in the q4w regimens, suggesting that, as the dose of tremelimumab increased above [redacted] mg/kg, a [redacted] rate of treatment related events may be anticipated. Further, the SAEs frequently attributed to immunotherapy, pneumonitis, colitis, and other immune-mediated events, were more commonly seen in cohorts using either [redacted] or [redacted] mg/kg of tremelimumab compared to the [redacted] mg/kg dose cohorts. Together, these data suggest that a combination using a tremelimumab dose [redacted] mg/kg appeared to [redacted] the rate of toxicity when combined with durvalumab. As a result, all combination doses utilizing either the [redacted] or [redacted] mg/kg doses of tremelimumab were eliminated in the final dose selection.
In contrast, cohorts assessing higher doses of durvalumab with a constant dose of tremelimumab did not show an increase in the rate of AEs. The data suggested that increasing doses of durvalumab may not impact the safety of the combination as much as the tremelimumab dose. Further, safety data between the [redacted] and [redacted] mg/kg cohorts were similar, with no change in safety events with increasing dose of durvalumab .

In Study D4190C00006, of all treatment cohorts, the cohort of patients treated in the [redacted] mg/kg durvalumab + [redacted] mg/kg tremelimumab group had a tolerable safety profile, but still showed [redacted] evidence of clinical activity. [redacted] were reported in this cohort. Preliminary clinical activity of the durvalumab (MEDI4736) and tremelimumab combination did not appear to change with increasing doses of tremelimumab. The [redacted] and [redacted] mg/kg durvalumab q4w cohorts demonstrated objective responses at all doses of tremelimumab, and increasing doses of tremelimumab did not provide deeper or more rapid responses. Efficacy data suggested that the [redacted] mg/kg durvalumab + [redacted] mg/kg tremelimumab dose cohort may demonstrate [redacted] clinical activity to other dose combinations. Of the [redacted] patients in this cohort, there wa[redacted] patient ([redacted]%) with a complete response (CR)[redacted] patients [redacted]%) with partial response (PR), [redacted] patients [redacted]%%) with stable disease (SD)[redacted] patient

CCI %) with an unconfirmed PR and CCI patients CCI%) with PD. CCI patients were not evaluable for response.

All together, the data suggested that a CCI mg/kg durvalumab + CCI mg/kg tremelimumab dose combination should be selected for further development.
Refer to the current durvalumab Investigator's Brochure for a complete summary of non-clinical and clinical information on the durvalumab + tremelimumab combination, including safety, efficacy and pharmacokinetics.

2.6.3.2 Study D4190C00010

Study D4190C00010 is a Phase 1 study of durvalumab in combination with tremelimumab in patients with advanced solid tumors.

As of a cutoff date of 10 March 2017, a total of 320 immunotherapy-naive subjects with advanced solid tumors have been treated in this study. Of these subjects CCI have received durvalumab at CCI mg/kg q2w for 12 months in combination with tremelimumab CCI mg/kg q4w for 7 doses and then every 12 weeks (q12w) for 2 doses. Included amongst the subjects receiving durvalumab at CCI mg/kg q4w for 12 months in combination with tremelimumab CCI mg/kg q4w for 7 doses and then q12w for 2 doses (n=45) were 30 subjects in the small-cell lung cancer cohort.

Overall, AEs (all grades, regardless of causality) reported in CCI % subjects by CCI order of frequency, were fatigue,, nausea, diarrhoea, pruritus, anemia, vomiting, deceased appetite, constipation, abdominal pain, dyspnea, pyrexia, back pain , , , , andhyponatraemia. The treatment-related AEs (all grades) reported in CCI % of patients, were fatigue, pruritus, diarrhoea, nausea, rash maculo-papular and hypothyroidism. A total of CCI % of patients had treatment-related Grade 3 or 4 AEs. The most common treatment-related Grade 3 or 4 AE were lipase increased, amylase increased, colitis and diarrhoea. SAEs were reported in CCI patients (CCI %); treatment-related SAEs were reported in CCI % of patients. The most frequent treatment-related SAEs were colitis and diarrhoea. A total of CCI patients (CCI %) experienced events with a CCI outcome; CCI of which were attributed to underlying disease and considered by the investigator as not related to durvalumab and tremelimumab. Two deaths were due to treatment-related AEs (pulmonary haemorrhage and colitis).

As of 20 October 2017, a total of 30 patients with SCLC received study treatment in Study 10. 19 of these patients were platinum resistant/refractory. CCI patients reported ≥1 treatment-related AE; the most common were fatigue and pruritus CCI patients had grade 3/4 treatment-related AEs. CCI patients discontinued due to treatment-related AEs and there wer CCI treatment-related deaths.

Confirmed ORR was CCI % (CCI), including 3 platinum resistant/refractory patients (1 CR with 2 prior therapies, 2 PR each with 1 prior treatment). Disease control rate at 16 weeks was CCI % (CCI). Median PFS was CCI months

([redacted]), median OS was [redacted] months ([redacted]), and 12-month OS rate was [redacted]

Refer to the current durvalumab IB for a complete summary of non-clinical and clinical information on the durvalumab + tremelimumab combination, including safety, efficacy, and PK.

2.6.4 Rationale for four cycles of combination therapy followed by durvalumab monotherapy

Long-term follow up on melanoma patients treated with ipilimumab, an anti-CTLA-4-targeting antibody (dosed every 3 weeks [q3w] for 4 doses and then discontinued), shows that patients responding to ipilimumab derive long-term benefit, with a 3-year overall survival (OS) rate of approximately 22%. Furthermore, the survival curve in this population reached a plateau at 3 years and was maintained through 10 years of follow up (Brahmer et al 2014, Schadendorf et al 2013).

Data from Study D4190C00006 (Phase I trial in NSCLC patients using the combination of durvalumab and tremelimumab) also show an approximately dose-proportional [redacted] in PK exposure for durvalumab over the dose range of [redacted] mg/kg durvalumab Q4W or Q2W. (For further information on PK observations in Study 006, please see the current IB).

The observed durvalumab PK data from the combination study were well in line with the predicted monotherapy PK data (5th median and 95th percentiles) for a Q4W regimen.

The durvalumab + tremelimumab combination regimen will be administered q4w for up to a total of 4 doses/cycles followed by durvalumab monotherapy q4w, until PD and Investigator confirmation that the patient is no longer receiving clinical benefit from the treatment, or for other discontinuation criteria. Note that patients whose weight falls to 30 kg or below will not receive fixed-dosing, instead this will switch to weight based dosing; equivalent to [redacted] mg/kg durvalumab and [redacted] mg/kg tremelimumab.

2.6.5 Durvalumab monotherapy dose rationale

A durvalumab) dose of [redacted] mg/kg q4w is supported by in vitro data, non-clinical activity, clinical PK/pharmacodynamics, biomarkers, and activity data from Study 1108 in patients with advanced solid tumors and from a Phase I trial performed in Japanese patients with advanced solid tumor (D4190C00002).

2.6.5.1 Durvalumab monotherapy Pharmacokinetic/Pharmacodynamic data

Based on available PK/pharmacodynamic data from ongoing Study 1108 with doses ranging from [redacted] mg/kg q2w or [redacted] mg/kg q3w, durvalumab exhibited non-linear (dose dependent) PK consistent with target-mediated drug disposition. The PK approached linearity a[redacted] mg/kg q2w, suggesting near complete target saturation (membrane-bound and sPD-L1), and further shows that the durvalumab administration frequency can be adapted to a particular regimen given the linearity seen at doses higher than [redacted] mg/kg. The expected half life with dose[redacted] mg/kg q2w is approximately 21 days. A dose-dependent suppression in peripheral

sPD-L1 was observed over the dose range studied, consistent with engagement of durvalumab with PD-L1. A CCI level of immunogenicity has been observed. No patients have experienced CCI disease following exposure to durvalumab (for further information on immunogenicity, please see the current durvalumab IB).

A population PK model was developed using the data from Study 1108 at doses of 0.1 to 10 mg/kg q2w or 15 mg/kg q3w (Fairman et al 2014). Multiple simulations indicate that a similar overall exposure is expected following both CCI mg/kg q2w and CCI mg/kg q4w regimens, as represented by AUC_{ss} (4 weeks). Median $C_{max,ss}$ is expected to be higher with CCI mg/kg q4w (CCI fold) and median $C_{trough,ss}$ is expected to be higher with CCI mg/kg q2w (CCI -fold).

Clinical activity with the CCI mg/kg q4w dosing regimen is anticipated to be consistent with CCI mg/kg q2w with the proposed similar dose of CCI mg/kg q4w expected to:

- Achieve complete target saturation in majority of patients.
- Account for anticipated variability in PK, pharmacodynamics, and clinical activity in diverse cancer populations.
- Maintain sufficient PK exposure in case of anti-drug antibody (ADA) impact.
- Achieve PK exposure that yielded maximal antitumor activity in animal models.

Given the similar Area under the plasma drug concentration-time curve (AUC) and modest differences in median peak and trough levels at steady state, the observation that both regimens maintain complete sPD-L1 suppression at trough level, and the available clinical data, the CCI mg/kg q4w and CCI mg/kg q2w regimens are expected to have similar efficacy and safety profiles, supporting further development with a dose of CCI mg/kg q4w.

2.6.5.2 Clinical experience with durvalumab

Refer to the current durvalumab IB for a complete summary of clinical information including safety, efficacy, and PK at the 20 mg/kg q4w regimen.

2.6.6 Rationale for fixed dosing of durvalumab and tremelimumab

A population PK model was developed for durvalumab using monotherapy data from a Phase I study (Study 1108; N=292; doses=CCI mg/kg to CCI mg/kg q2w or CCI mg/kg q3w; solid tumors). Population PK analysis indicated only minor impact of body weight on the PK of durvalumab (coefficient of CCI). The impact of body weight-based (CCI mg/kg q2w) and fixed dosing (CCI mg q2w) of durvalumab was evaluated by comparing predicted steady-state PK concentrations (5^{th}, median and 95^{th} percentiles) using the population PK model. A fixed dose of CCI mg was selected to approximate CCI mg/kg (based on median body weight of ~75 kg). A total of 1000 patients were simulated using body weight distribution of 40 kg to 120 kg. Simulation results demonstrate that body weight-based and fixed dosing regimens

yield similar median steady state PK concentrations with slightly less overall between-patient variability with fixed dosing regimen.

Similarly, a population PK model was developed for tremelimumab using data from Phase I through Phase III studies (N = 654; doses = CCI mg/kg to 15 mg/kg q4w or every 90 days; metastatic melanoma) [Wang et al 2014]. A population PK model indicated minor impact of body weight on PK of tremelimumab (coefficient of ≤0.5). The body weight-based (1 mg/kg q4w) and fixed-dosing (75 mg/kg q4w; based on median body weight of ~75 kg) regimens were compared using predicted PK concentrations (5th, median, and 95th percentiles) using a population PK model in a simulated population of 1000 patients with body weight distribution of 40 kg to 120 kg. Similar to durvalumab , simulations indicated that both body weight-based and fixed-dosing regimens of tremelimumab yielded similar median steady state PK concentrations with slightly less between-patient variability with fixed dosing regimen.

Similar findings have been reported by others (Ng et al 2006, Wang et al 2009, Zhang et al 2012, Narwal et al 2013). Wang and colleagues investigated 12 mAbs and found that fixed and body-size based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies (Wang et al 2009). In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-patient variability in PK/pharmacodynamics parameters (Zhang et al 2012).

A fixed dosing approach is preferred by the prescribing community due to ease of use and low dosing errors. Given the expectation of similar PK exposure and variability, it was considered feasible to switch to a fixed dosing regimen. Based on average body weight of 75 kg, a fixed dose of 1500 mg q4w durvalumab (equivalent to CCI mg/kg) and a fixed dose of CCI mg q4w tremelimumab (equivalent to CCI mg/kg) are included in the current study.

Fixed dosing of durvalumab and tremelimumab will not be applied for patients who weigh 30 kg or less; such patients will receive weight based dosing due to the regulatory limits for endotoxin exposure. The durvalumab endotoxin specification (CCI endotoxin unit [EU]/mg protein) supports the CCI mg fixed durvalumab dose for a 1 hour infusion for a patient > 30 kg. This ensures the USP criteria of no more than 5.0 EU/kg body weight/hour is met. As the equivalent to the CCI mg dose, patients weighing ≤ 30 kg will receive a CCI mg/kg dose.

2.6.7 Rationale for study endpoints

The rationale for study endpoints is provided in Section 2.2.3 of the master protocol.

2.7 Benefit/risk and ethical assessment

The unmet need in refractory or resistant ED-SCLC is described in Sections 2.1 and 2.3 of the master protocol. Additional information on the potential benefits of durvalumab and tremelimumab and an assessment of the potential and known risks can also be found in the respective IBs for each agent.

2.7.1 Potential benefits

2.7.1.1 Durvalumab

The majority of the safety and efficacy data currently available for durvalumab are based on the first-in-human, single-agent study (Study 1108) in patients with advanced solid tumors. Overall, as of 24 October 2016, 970 patients had been treated with durvalumab 10 mg/kg q2w.

CCI [redacted]

Data from patients with SCLC in the durvalumab monotherapy Phase I Study 1108, although limited (n=21), CCI [redacted]

2.7.1.2 Durvalumab + tremelimumab

Available data suggest that the combination of agents targeting PD-1/PD-L1 and CTLA-4 may have profound and durable benefits in patients with melanoma (Wolchok et al 2013). Furthermore, preliminary efficacy data from Study D4190C00006 have demonstrated that this combination is clinically active and well-tolerated. As of 28 February 2017,, 166 patients with at least 24 weeks of follow-up were evaluable for response across the following patient cohorts: dose escalation (advanced NSCLC); and dose-expansion Cohort A (treatment-naive NSCLC selected by PD-L1 status), Cohort B co-administration (immunotherapy-naïve, 1L or 2L patients with NSCLC) and Cohort B sequential administration (2L patients with non-squamous NSCLC). CCI [redacted]

As of 20 October 2017,30 patients with ED-SCLC were treated on Study D4190C00010 with the combination of durvalumab (20 mg/kg) and tremelimumab (1 mg/kg) administered q4w for 4 doses, followed by durvalumab alone at a dose of 10 mg/kg q2w for up to a total of 12 months. 19 of these patients were platinum resistant/refractory. Confirmed ORR was

CCI [redacted]

2.7.2 Identified and potential risks

mAbs directed against immune checkpoint proteins, such as PD-L1, as well as those directed against PD-1 or CTLA-4, aim to boost endogenous immune responses directed against tumor cells. By stimulating the immune system, however, there is the potential for adverse effects on other tissues.

Most adverse drug reactions seen with the immune checkpoint inhibitor class of agents are thought to be due to the effects of inflammatory cells on specific tissues. These risks are generally events with a potential inflammatory or immune mediated mechanism and which may require more frequent monitoring and/or unique interventions such as immunosuppressants and/or endocrine therapy. These immune mediated effects, can occur in nearly any organ system, and are most commonly seen as gastrointestinal AEs such as colitis and diarrhoea, pneumonitis/interstitial lung disease (ILD), hepatic AEs such as hepatitis and liver enzyme elevations, skin events such as rash and dermatitis and endocrinopathies including hypo- and hyper-thyroidism.

2.7.2.1 Durvalumab

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

For information on all identified and potential risks with durvalumab please always refer to the current version of the durvalumab IB.

In monotherapy clinical studies AEs at an incidence of $\geq$ 20% include events such as fatigue, cough,decreased appetite, dyspnea, and nausea. Approximately 10% of patients discontinued the drug due to an AE. Please see the current version of the IB for a detailed summary of the monotherapy data including AEs, SAEs, and CTC Grade 3 to 5 events reported across the durvalumab program.

The majority of treatment-related AEs were manageable with dose delays, symptomatic treatment, and in the case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated toxicity (see Section 7.5).

A detailed summary of durvalumab monotherapy AE data can be found in the current version of the durvalumab IB.

2.7.2.2 Tremelimumab

Risks with tremelimumab monotherapy include, but are not limited to, GI effects (colitis, diarrhoea, enterocolitis and intestinal perforation), endocrine disorders (hypo and hyperthyroidism, hypophysitis and adrenal insufficiency), skin effects (rash, and pruritus), elevations in lipase and amylase and clinical manifestations of pancreatitis, hepatic events (including immune mediated hepatitis, and liver enzyme elevations); pneumonitis and ILD; neurotoxicity (including encephalitis, peripheral motor and sensory neuropathies, Guillain-Barre syndrome),thrombocytopenia, anemia and neutropenia; infusion-related reactions, and allergic reactions; renal events (including nephritis, /autoimmune nephritis autoimmune arthritis, Sjogren's syndrome, giant cell temporal arteritis, and ulcerative colitis; hyperglycemia and diabetes mellitus.

For information on all identified and potential risks with tremelimumab please always refer to the current version of the tremelimumab IB.

In monotherapy clinical studies AEs reported at an incidence of > 20% include events such as diarrhea, nausea, fatigue, pruritus, decreased appetite, rash, vomiting, and dyspnoea. Approximately 16% of patients experienced an AE that resulted in permanent discontinuation of tremelimumab and approximately 45% of patients experienced an SAE.

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

2.7.2.3 Durvalumab + tremelimumab

The safety of durvalumab + tremelimumab combination therapy was initially evaluated in the ongoing dose escalation and dose expansion Study D4190C00006, in patients with NSCLC, and is being studied in a number of other ongoing clinical trials in a number of different indications, and has to date shown a manageable safety and tolerability profile.

The types of risks with the combination of durvalumab + tremelimumab (based on an equivalent durvalumab dose of 20m/kg and a tremelimumab dose of 1mg/kg) are similar to those for durvalumab and tremelimumab monotherapy. Emerging data from study D4190C00006, other studies evaluating the combination, and from combinations of other agents in the same class indicate an increased frequency and/or severity of some of these immune-mediated toxicities.

For information on all identified and potential risks with the durvalumab + tremelimumab combination please always refer to the current version of the durvalumab IB.

In durvalumab +tremelimumab combination studies at the dose of durvalumab 20mg/kg and tremelimumab 1mg/kg AEs reported at an incidence $\geq$ 20% included events such as fatigue, diarrhoea, nausea, decreased appetite, pruritus, dyspnea, constipation, and anemia.

Approximately 15% of patients experienced an AE that resulted in permanent discontinuation of study drug and approximately 15% of patients experienced an SAE that was considered to be related to durvalumab and tremelimumab by the study investigator.

Please see the current version of the durvalumab IB for a detailed summary of combination therapy data, including AEs, SAEs, and CTC Grade 3 to 5 events reported across the durvalumab program, including durvalumab in combination with tremelimumab.

2.7.3 Overall benefit risk

The prognosis of ED-SCLC remains very poor, a with median OS of about 10 months; patients who progress through first-line chemotherapy or within 90 days of completing chemotherapy have even worse prognosis; median OS is less than 6 months (von Pawel et al 2014). There is only 1 treatment approved for patients who are refractory or resistant to first-line chemotherapy, which has shown very limited activity. This has indicated a significant unmet medical need for improving treatment outcomes for patients with refractory or resistant ED-SCLC. Treatment with durvalumab and/or tremelimumab has shown activity in several tumor types including SCLC. The safety profile of durvalumab in combination with tremelimumab is generally well tolerated; the safety monitoring and guidance are in place to manage potential toxicities. Therefore, the benefit:risk ratio for this Phase II study supports the combined administration of durvalumab and tremelimumab to patients with documented refractory or resistant ED-SCLC.

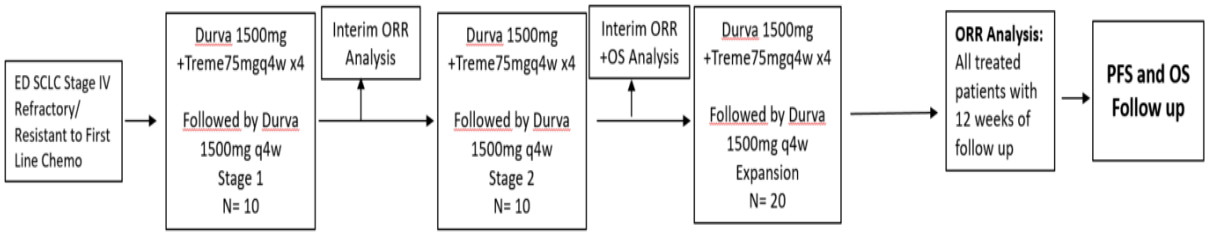
2.8 Study design

Arm A will investigate the preliminary efficacy, safety and tolerability of durvalumab in combination with tremelimumab followed by durvalumab monotherapy given IV to patients who progress during first line chemotherapy or those who progress within 90 days of completing first line-chemotherapy.

For Arm A, up to 40 eligible patients will be enrolled, and all patients will receive:

Durvalumab 1500 mg + tremelimumab 75 mg via IV infusion q4w, starting on Week 0, for up to a total of 4 doses/cycles followed by durvalumab monotherapy 1500 mg via IV infusion q4w, starting on Week 16 until confirmed PD and Investigator confirmation that the patient is no longer receiving clinical benefit from the treatment, or for other discontinuation criteria. If a patient's weight falls to 30 kg or below, the patient should receive weight-based dosing after discussion between Investigator and Study Physician, until the weight improves to > 30 kg, at which point the patient should start receiving the fixed dosing of durvalumab 1500 mg and tremelimumab 75 mg q4w (during the combination phase of treatment). The equivalent weight based doses to the fixed doses are 20 mg/kg of durvalumab and 1mg/kg tremelimumab q4w.

Appendix A Figure 1 Arm A Study design



Durva Durvalumab ; ED Extensive stage disease small-cell lung cancer; ORR Overall response rate; PFS Progression-free survival; q4w Every 4 weeks; Treme Tremelimumab.

3. STUDY OBJECTIVES

3.1 Primary objective

See Section 3.1 of the master protocol.

3.2 Secondary objectives

See Section 3.2 of the master protocol.

3.3 Safety objectives

See Section 3.3 of the master protocol.

3.4 Exploratory objectives

See Section 3.4 of the master protocol.

4. PATIENT SELECTION, ENROLLMENT, RANDOMIZATION, RESTRICTIONS, DISCONTINUATION, AND WITHDRAWAL

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

4.1 Inclusion criteria

1. Male or female ≥18 years at the time of screening.

2. Written informed consent and any locally required authorization (eg, Health Insurance Portability and Accountability Act in the US, EU Data Privacy Directive in the EU) obtained from the patient/legal representative prior to performing any protocol-related procedures, including screening evaluations.

3. Histologically or cytologically documented extensive disease American Joint Committee on Cancer Stage IV SCLC (T any, N any, M1 a/b) at initial diagnosis, also including patients with:

    - T3-4 due to multiple lung nodules that are too extensive or have tumor/nodal volume that is too large to be encompassed in a tolerable radiation plan.

    - Biopsy-proven mixed SCLC and NSCLC histology

    - Brain metastases; must be asymptomatic or treated and stable off steroids and anti-convulsants for at least 1 month prior to study treatment. Patients with suspected brain metastases at screening should have a computed tomography (CT)/magnetic resonance imaging (MRI) of the brain prior to study entry.

4. Patients must have demonstrated progressive disease (PD) either during first-line platinum-based chemotherapy (platinum refractory) or within 90 days of completing platinum-based chemotherapy (platinum resistant), and have not received further treatment apart from first-line platinum-based chemotherapy. Patients should be enrolled within 90 days of progression in order to be accepted into the study.

5. World Health Organization (WHO)/Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 1 at enrollment for the first 10 patients recruited to this arm (see Section 6.3.1 of master protocol for WHO/ECOG assessment parameters). This can be extended to Performance Status 0 to 2 if the arm recruits an additional 10 patients.

6. At least 1 lesion, not previously irradiated, that can be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes, which must have a short axis ≥15 mm) with CT or MRI and that is suitable for accurate repeated measurements as per RECIST 1.1 guidelines.

7. No prior exposure to immune-mediated therapy including, but not limited to, other anti-CTLA-4, anti-PD-1, anti-PD-L1, and anti programmed cell death ligand 2 (anti-PD-L2) antibodies, excluding therapeutic anticancer vaccines.

8. Body weight >30 kg.

9. Mandatory provision of a fresh or archival (<1 year) tumour biopsy (or at least 15-20 × 5 μm newly cut [within 3 months] unstained slides).

10. Willingness and ability to comply with study and follow-up procedures.

11. Life expectancy of at least 8 weeks.

12. Adequate organ and marrow function as defined below

    - Hemoglobin ≥9.0 g/dL
    - Absolute neutrophil count ≥1.0×10^9 /L (Use of granulocyte-colony stimulating factor is not permitted to raise neutrophils for screening.)
    - Platelet count ≥75×10^9/L
    - Serum bilirubin ≤1.5× upper limit of normal (ULN). This will not apply to patients with confirmed Gilbert's syndrome, who will be allowed in consultation with their physician.
    - In patients without hepatic metastasis: ALT and aspartate aminotransferase (AST) ≤2.5× ULN
    - In patients with hepatic metastases, ALT and AST ≤5× ULN
    - Calculated creatinine clearance (CL) >40 mL/min as determined by Cockcroft-Gault (using actual body weight)

      Males:

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

      Females:

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

13. Evidence of post-menopausal status or negative urinary or serum pregnancy test for female pre-menopausal patients. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

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

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

4.2 Exclusion criteria

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

2. Previous enrollment in the present study.

3. Participation in another clinical study with an investigational product (IP) during the last 4 weeks.

4. Prior randomization or treatment in a previous durvalumab and/or tremelimumab clinical study regardless of treatment arm assignment.

5. Concurrent enrollment in another clinical study unless it is an observational (non-interventional) clinical study or the follow-up period of an interventional study.

6. Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of IP. Note: Local surgery of isolated lesions for palliative intent is acceptable where this does not affect assessment of target lesions.

7. Any condition that, in the opinion of the Investigator, would interfere with the evaluation of the IP or interpretation of patient safety or study results, including but not limited to ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhea or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs from the study medications, or compromise the ability of the patient to give written informed consent.

8. Active autoimmune disease, including a paraneoplastic syndrome of autoimmune nature, requiring systemic treatment other than chemotherapy for SCLC, within the past 3 months

or a documented history of clinically severe autoimmune disease or a syndrome that requires or required systemic steroids or immunosuppressive agents.

9. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [eg, colitis or Crohn's disease]), diverticulitis with the exception of (diverticulosis), celiac disease, systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome (granulomatosis with polyangiitis), Grave's disease, rheumatoid arthritis, hypophysitis, uveitis, etc. The following are exceptions to this criterion:

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

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

11. Persistent toxicities (>Common Terminology Criteria for Adverse Events [CTCAE] Grade 2) caused by previous cancer therapy. Any unresolved toxicity (National Cancer Institute [NCI] CTCAE Grade >2) from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory results defined in the inclusion criteria.

    - Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab or tremelimumab may be included only after consultation with the Study Physician.
    - Patients with Grade >2 neuropathy will be evaluated on a case-by-case basis after consultation with the Study Physician

12. Any concurrent chemotherapy, immunotherapy (eg, a CTLA-4, PD-1, or PD-L1 inhibitor), or biologic or hormonal therapy for cancer treatment. Concurrent use of hormones for

non-cancer-related conditions (eg, insulin for diabetes and hormone replacement therapy) is acceptable.

13. Receipt of any live attenuated vaccination within 30 days prior to study entry, while receiving durvalumab + tremelimumab, and within 30 days of receiving durvalumab ± tremelimumab.

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

    - Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra-articular injection)
    - Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent
    - Steroids as pre-medication for hypersensitivity reactions (eg, computed tomography [CT] scan pre-medication)

15. Radiation therapy to the chest and whole-brain irradiation must be completed at least 4 weeks prior to start of study treatment, and patients must have recovered from any acute adverse effects prior to start of study treatment. An exception to this is palliative radiotherapy for bone lesions and must be completed before the first dose of study treatment.

16. Past medical history of interstitial lung disease, drug-induced pneumonitis, radiation pneumonitis that required steroid treatment, or any evidence of clinically active interstitial lung disease.

17. History of hypersensitivity to active or inactive excipients of any investigational drug in the study or drugs with a similar chemical structure or class to those investigated in the study.

18. History of another primary malignancy except for:

    - Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of study drug and of low potential risk for recurrence
    - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
    - Adequately treated carcinoma in situ without evidence of disease (eg, cervical cancer in situ)

19. History of leptomeningeal carcinomatosis.

20. History of active primary immunodeficiency.

21. History of allogenic organ transplantation.

22. Spinal cord compression unless asymptomatic or treated and stable off steroids and anti-convulsants for at least 1 month prior to study treatment.

23. Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 90 days after the last dose of durvalumab monotherapy or 180 days after the last dose of durvalumab tremelimumab combination therapy.

4.3 Patient enrollment and randomization

See Section 4.3 of the master protocol.

4.4 Procedures for handling incorrectly enrolled or randomized patients

See Section 4.4 of the master protocol.

4.5 Methods for assigning treatment groups

Not applicable.

4.6 Restrictions

The following restrictions apply while the patient is receiving study treatment and for the specified times before and after (refer to Section 4.8 of the master protocol for restrictions applicable to all arms of study):

1. Female patient of child-bearing potential

    - Female patients of childbearing potential who are not abstinent and intend to be sexually active with a nonsterilized- male partner must use at least 1 **highly** effective method of contraception (Appendix A Table 1) from the time of screening throughout the total duration of the drug treatment and the drug washout period (180 days after the last dose of durvalumab + tremelimumab combination therapy or 90 days after the last dose of durvalumab monotherapy). Non-sterilised male partners of a female patient of childbearing potential must use male condom plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control. Female patients should also refrain from breastfeeding throughout this period.

2. Male patients with a female partner of childbearing potential

- Non-sterilized male patients who are not abstinent and intend to be sexually active with a female partner of childbearing potential must use a male condom plus spermicide from the time of screening throughout the total duration of the drug treatment and the drug washout period (180 days after the last dose of durvalumab + tremelimumab combination therapy or 90 days after the last dose of durvalumab monotherapy). However, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male patients should refrain from sperm donation throughout this period.

- Female partners (of childbearing potential) of male patients must also use a highly effective method of contraception throughout this period (Appendix A Table 1).

N.B Females of childbearing potential are defined as those who are not surgically sterile (ie, bilateral salpingectomy, bilateral oophorectomy, or complete hysterectomy) or post-menopausal.

3. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

    - Women <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution.

    - Women ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago .

4. Highly effective methods of contraception, defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly are described in Appendix A Table 1. Note that some contraception methods are not considered highly effective (e.g. male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non-copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding Cerazette/desogestrel which is considered highly effective]; and triphasic combined oral contraceptive pills).

5. Patients should not donate blood or blood components while participating in this study and through 180 days after receipt of the final dose of durvalumab + tremelimumab combination therapy or 90 days after receipt of the final dose of durvalumab or alternative anti-cancer therapy is started.

6. Restrictions relating to concomitant medications are described in the accountability section of this appendix.

Appendix A Table 1 Highly effective methods of contraception (less than 1% failure rate per year)

Barrier/Intrauterine methods	Hormonal methods
Copper T intrauterine device	Implants
Levonorgestrel-releasing intrauterine system (eg, MIRENA®)[a]	Hormone shot or injection
	Combined pill
	Minipill
	Patch
Intravaginal Devices	Ethinylestradiol/etonogestrel-releasing intravaginal devices e.g. NuvaRing®

[a] This is also considered a hormonal method.

4.7 Discontinuation of investigational product

Please also refer to Section 4.9 of the master protocol for discontinuation criteria applicable to all arms of the study. Additional discontinuation criteria applicable to Arm A are listed below:

- Grade ≥3 infusion reactions.
- Clinical progression, i.e. Investigator determination that the patient is no longer benefiting from treatment with IP, with or without radiological progression by RECIST 1.1.

4.7.1 Assessments following discontinuation of investigational product

Please also refer to Section 4.9.2 of the master protocol for assessments following discontinuation of IP applicable to all arms of the study.

Additional assessments following discontinuation of IP applicable to Arm A are listed below:

All SAEs occurring for up to 90 days after the last dose of study treatment must be recorded in the electronic case report form (eCRF).

4.8 Criteria for withdrawal

See Section 4.10 of the master protocol.

4.9 Discontinuation of the study

See Section 4.11 of the master protocol.

5. STUDY PLAN AND TIMING OF PROCEDURES

The procedures for the screening and the treatment periods in this study are presented in Appendix A Table 2. The procedures for the follow-up period are presented in Appendix A Table 3.

Patients may delay dosing under certain circumstances.

- Dosing may be delayed per Toxicity Management Guidelines, due to either an immune or a non-immune-related AE.
- If dosing must be delayed for reasons other than treatment-related toxicity, dosing will resume as soon as feasible
- Dosing intervals of subsequent cycles may be shortened as clinically feasible in order to gradually align treatment cycles with the schedule of tumor efficacy (RECIST) assessments. Subsequent time between 2 consecutive doses cannot be less than 22 days, based on the half-lives of durvalumab and tremelimumab (see current Investigator Brochures for durvalumab and tremelimumab).

Appendix A Table 2 Schedule of assessments for durvalumab + tremelimumab combination therapy, and durvalumab monotherapy treatment period

	Screening	C1	C2	C3	C4	C5	C6	C7	C8+ or PD	For details see
Week	**-4to-1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28, 32, 36, 40+ or PD**	
Day	**-28 to-1**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197, 225, 253, 281, 309, 337, 365, or PD**	
Window (days)	**NA**	**±1**	**(±3 days, tumor assessment ±7 days)**							
Informed consent: study procedures including biomarker sample collection[a]	X									Section 6 master protocol
Study Procedures										
Physical examination (full)	X									Section 6.2.2 master protocol
Targeted physical examination (based on symptoms)		X	X	X	X	X	X	X	X	Section 6.2.2 master protocol
Vital signs[b]	X	X	X	X	X	X	X	X	X	Section 6.2.4 master protocol and Section 6.2.2 Appendix A
ECG[c]	X	As clinically indicated								Section 6.2.3 master protocol
Concomitant medications	←----------→									Section 8.7 master protocol
Demography, including baseline characteristics and tobacco use	X									Section 6 master protocol

Appendix A Table 2 Schedule of assessments for durvalumab + tremelimumab combination therapy, and durvalumab monotherapy treatment period

	Screening	C1	C2	C3	C4	C5	C6	C7	C8+ or PD	For details see
Week	**-4to-1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28, 32, 36, 40+ or PD**	
Day	**-28 to-1**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197, 225, 253, 281, 309, 337, 365, or PD**	
Window (days)	**NA**	**±1**	**(±3 days, tumor assessment ±7 days)**							
Eligibility criteria	X									Sections 4.1 and 4.2 master protocol and Appendix A sections 4.1and 4.2
Laboratory assessments										
Clinical chemistry	X	X[d]	X	X	X	X	X	X	X	Table 4 Appendix A
Hematology	X	X[d]	X	X	X	X	X	X	X	Table 5 Appendix A
TSH (reflex free T_3, and free T_4[e])	X[q]	X	X	X	X	X	X	X	X	Table 4 Appendix A
Coagulation (PT/INR/PTT)	X	as clinically indicated								Table 5 Appendix A
Urinalysis	X	As clinically indicated								Table 6 Appendix A
Hepatitis B and C and HIV	X									Section 6.2.1 master protocol
Pregnancy test[f]	X	X	X	X	X	X	X	X	X	Section 6.2.1 master protocol
PK[o]										
Durvalumab PK sample (serum)[o]		X[g,o]	X[h,o]			X[h,o]				Section 6.4 Appendix A
Tremelimumab PK sample (serum)[o]		X[g,o]	X[h,o]			X[h,o]				Section 6.4 Appendix A

Appendix A Table 2 Schedule of assessments for durvalumab + tremelimumab combination therapy, and durvalumab monotherapy treatment period

	Screening	C1	C2	C3	C4	C5	C6	C7	C8+ or PD	For details see
Week	**-4to-1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28, 32, 36, 40+ or PD**	
Day	**-28 to-1**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197, 225, 253, 281, 309, 337, 365, or PD**	
Window (days)	**NA**	**±1**	**(±3 days, tumor assessment ±7 days)**							
Tremelimumab PK sample (serum) for patients who complete 4 combo doses-Follow up sample (12 weeks after last dose of tremelimumab)[o]								X[h,o]		Section 6.4 Appendix A
Monitoring										
WHO/ECOG performance status	X	X	X	X	X	X	X	X	X	Section 6.3.1 master protocol
AE/SAE assessment[i]	←----------								----------→	Section 7 master protocol
IP Administration										
Durvalumab (combination therapy)[j, k]		X	X	X	X					Section 8.1.1 master protocol
Tremelimumab[j, k]		X	X	X	X					Section 8.1.1 master protocol
Durvalumab (monotherapy)[k]						X	X	X	X	Section 8.1.1 master protocol
Study Laboratory Assessments										
ADA sampling to identify ADA responses in patient circulation[o]		X[o]	X[o]			X[o]				Section 6.3 Appendix A

Appendix A Table 2 Schedule of assessments for durvalumab + tremelimumab combination therapy, and durvalumab monotherapy treatment period

	Screening	C1	C2	C3	C4	C5	C6	C7	C8+ or PD	For details see
Week	**-4to-1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28, 32, 36, 40+ or PD**	
Day	**-28 to-1**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197, 225, 253, 281, 309, 337, 365, or PD**	
Window (days)	**NA**	**±1**	**(±3 days, tumor assessment ±7 days)**							
mRNA[o]		X[o]								Sections 6.6.1.2 and 6.6.1.4 master protocol
Circulating tumour DNA		X		X						Section 6.3 Appendix A
Tumor biopsy (newly acquired or archival ≤1 years old)[a,p]	X									Section 6.6 master protocol
Tumor evaluation (CT or MRI) [RECIST 1.1][l, m]	X			X	X	q8w ± 1week after week 12 until confirmed objective disease progression/death (whichever comes first).				Section 6.1 master protocol

[a] If laboratory or imaging procedures were performed for other reasons prior to signing consent, these can be used for screening purposes with consent of the patient. However, all screening laboratory and imaging results must have been obtained within 28 days of enrollment.

[b] Body weight is recorded at each visit along with vital signs. Vital signs are recorded at every clinic visit. Vital signs should be measured separately for both drugs. For details please check Section 6.2.2 Appendix A.

[c] Any clinically significant detected require triplicate ECG results.

[d] If screening laboratory assessments are performed within 3 days prior to Day 1 (first infusion day), they do not need to be repeated at Day 1. Serum or plasma chemistry, hematology, and/or LFT monitoring may be performed more frequently if clinically indicated.

[e] Free T3 and free T4 will be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.

[f] For women of childbearing potential only. A urine or serum pregnancy test is acceptable. Women of childbearing potential are required to have a pregnancy test within 7 days prior to the first dose of study drug and then every 4 weeks. Pregnancy test may occur on Day 1, but results must be available and reviewed by the treating physician or Investigator prior to commencing an infusion.

[g] Within 10 minutes of the end of infusion.

[h] Up to 60 minutes pre-dose.

[i] For AEs/SAEs reported during screening, additional information such as medical history and concomitant medications may be needed.

[j] During the combination portion of treatment, tremelimumab will be administered first; the durvalumab infusion will start approximately 1 hour (maximum 2 hours) after the end of the tremelimumab infusion. If there are no clinically significant infusion reactions with the first cycle, and at the discretion of the Investigator, then for all other cycles, the durvalumab can be given immediately after the tremelimumab infusion has finished.

[k] Results for serum or plasma chemistry and LFT monitoring must be available before commencing an infusion (within 3 days) and reviewed by the treating physician or Investigator prior to dosing.

[l] RECIST 1.1 assessments will be performed on images from CT (preferred) or MRI, each preferably with IV contrast of the chest, abdomen (including liver and adrenal glands), and pelvis. Pelvic imaging is recommended only when primary or metastatic disease in the pelvic region is likely. Additional anatomy should be imaged based on signs and symptoms of individual patients at baseline and follow-up. Baseline assessments should be performed no more than 28 days before the date of enrollment and, ideally, should be performed as close as possible to and prior to the start of the initial dose of IP. The confirmatory scans should be performed preferably at the next scheduled imaging visit and no less than 4 weeks after the prior assessment of CR/PR or PD (in the absence of clinically significant deterioration). If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their next scheduled visit.

[m] Patients will have scans done at Week 8, 12, and then q8w thereafter (relative to the date of first dose) until confirmed objective disease progression.

[o] Pharmacokinetic, ADA and mRNA samples will be collected from patients recruited into stage 1 and 2 only. Collection of pharmacokinetic, ADA and mRNA samples are not required for patients recruited into the expansion cohorts.

[p] If available, patient's newly acquired or archival ≤1 year old tumor samples should be collected. For patients enrolled into the expansion cohort, provision of a tumour tissue sample is mandated prior to commencing study treatment. If sufficient archival tumour tissue is not available the patient will be invited to provide a fresh biopsy, following registration but prior to any protocol treatment. Adequate tissue is defined as availability of a tumour block or 15 to 20 unstained slides, each 4 to 5 microns thick and cut within 3 months of study treatment from an FFPE block from an archival sample ≤1 year old.

[q] Samples can be collected within 3days prior to the visit.

[r] Samples for CCI should be collected at baseline any time up to C1D1 as long as this is pre-dose. One further on-treatment sample is required at C3.

Note: All assessments on treatment days are to be performed prior to infusion, unless otherwise indicated.

ADA Anti-drug antibody; AE Adverse event; C Cycle; CR Complete response; CT Computed tomography; CCI; DNA Deoxyribonucleic acid; ECG Electrocardiogram; ECOG Eastern Cooperative Oncology Group; EOT End of treatment; HIV Human immunodeficiency virus; IP Investigational product; IV Intravenous; LFT Liver function test; MRI Magnetic resonance imaging; NA Not applicable; PD Progressive disease; PK Pharmacokinetic; PR Partial response; q8w Every 8 weeks; RECIST 1.1 Response Evaluation Criteria in Solid Tumors, version 1.1; SAE Serious adverse event; T3 Triiodothyronine; T4 Thyroxine; TSH Thyroid-stimulating hormone; WHO World health Organization.

Appendix A Table 3 Schedule of assessments: completed/discontinued treatment with durvalumab + tremelimumab combination therapy, and durvalumab monotherapy

Evaluation	Time since last dose of IP								
	Day (±3)	Months (±1 week)						12 months and every 2 months (±2 weeks)	For details see
	30	2	3	4	6	8	10		
Physical examination (full)[a]	X								Section 6.2.2 master protocol
Vital signs (temperature, respiratory rate, blood pressure, and pulse)	X								Section 6.2.4 master protocol
Weight	X								Section 6.2.4 master protocol
Pregnancy test[b]	X	As clinically indicated							Section 6.2.1 master protocol
AE/SAE assessment	X	X	X						Section 7 master protocol
Concomitant medications	X	X	X						Section 8.7 master protocol
WHO/ECOG performance status	At timepoints consistent with tumor assessments; at 30, 60, and 90 days; and then at initiation of subsequent anticancer therapy[c]								Section 6.3.1 master protocol
Details of subsequent anticancer therapy to be recorded in eCRF[d,e]	<----------							---------->	NA
Survival status[f]		X	X	X	X	X	X	X	Section 6.1.1 master protocol
Hematology	X	X	X						Table 5 Appendix A
Clinical chemistry	X	X	X						Table 4 Appendix A
TSH (reflex free T_3, and free T_4[g])	X	X	X						Table 4 Appendix A

Appendix A Table 3 Schedule of assessments: completed/discontinued treatment with durvalumab + tremelimumab combination therapy, and durvalumab monotherapy

Evaluation	Time since last dose of IP								
	Day (±3)	Months (±1 week)						12 months and every 2 months (±2 weeks)	For details see
	30	2	3	4	6	8	10		
Durvalumab PK sample (serum)[i]			X[i]						Section 6.4 master protocol
Tremelimumab PK sample (serum)i			(X)[j,i]						Section 6.4 master protocol
Immunogenicity assessment (ADA sampling) to identify ADA responses[i]			X[i]		X[i]				Section 6.3 Appendix A
Tumor assessment (CT or MRI) (RECIST 1.1)[h]	Tumor assessments should be performed q8w ± 1week after week 12 until confirmed objective disease progression/death (whichever comes first).								Section 6.1 master protocol

[a] Physical examinations are described in Section 6.2.2 of the master protocol.
[b] For women of childbearing potential only. A urine or serum pregnancy test is acceptable.
[c] WHO/ECOG performance status should also be collected at other site visits that the patient attends, if appropriate site staff are available to collect such information. In addition, WHO/ECOG performance status should be provided when information on subsequent anticancer therapy is provided, where possible.
[d] Details of any treatment for SCLC (including surgery) post the last dose of IP must be recorded in the eCRF. At minimum, collect the start date and description of the subsequent anticancer therapy.
[e] For patients who discontinue their assigned IP following confirmed progression, available readings of CT/MRI from local practice will be collected from patients' medical charts while information on subsequent anticancer treatment is collected.
[f] Patients may be contacted in the week following data cutoffs to confirm survival status. Details of any treatment for SCLC (including surgery) post the last dose of IP must be recorded in the eCRF.
[g] Free T_3 and free T_4 will be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.
[h] Only for patients yet to progress. RECIST 1.1 assessments will be performed on images from CT (preferred) or MRI, each preferably with IV contrast, of the chest, abdomen (including liver and adrenal glands), and pelvis. Pelvic imaging is recommended only when primary or metastatic disease in the pelvic region is likely. Additional anatomy should be imaged based on signs and symptoms of individual patients. The confirmatory scans should be performed preferably at the next scheduled imaging visit and no less than 4 weeks after the initial assessment of CR/PR or PD (in the absence of clinically significant deterioration). If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits (relative to the date of first IP administration
[i] Pharmacokinetic, ADA and CCI samples will be collected from patients recruited into stage 1 and 2 only. Collection of pharmacokinetic, ADA and CCI samples are not required for patients recruited into the expansion cohort.Details for processing, handling, and shipping are in the Laboratory Manual.
[j] To be collected only, if the patient has completed/discontinued treatment with durvalumab + tremelimumab combination therapy in stages 1 or 2 and no follow up tremelimumab PK sample was taken yet.

ADA Anti-drug antibody; AE Adverse event; CR Complete response; CT Computed tomography; ECOG Eastern Cooperative Oncology Group; eCRF Electronic case report form; IP Investigational product; IV Intravenous; MRI Magnetic resonance imaging; NA Not applicable; PD Progressive disease; PR Partial response; q8w Every 8 weeks; RECIST 1.1 Response Evaluation Criteria in Solid Tumors, version 1.1; SAE Serious adverse event; SCLC Small-cell lung cancer; T_3 Triiodothyronine; T_4 Thyroxine; TSH Thyroid-stimulating hormone; WHO World health Organization.

5.1 Enrollment/screening period

All screening and enrollment procedures will be performed according to the assessment schedule in Appendix A Table 2. Demographic data and other characteristics will be recorded including date of birth or age, gender, smoking history, and race/ethnicity, according to local regulations. A standard medical and surgical history will be obtained.

Written informed consent and any locally required privacy act document authorization must be obtained prior to performing any protocol-specific procedures, including screening/baseline evaluations. If laboratory or imaging procedures were performed for other reasons prior to signing consent, these can be used for screening purposes with consent of the patient. However, all screening laboratory and imaging results must have been obtained within 28 days of enrollment. All patients will have the option to provide consent to supply a sample of their tumor (archived or newly acquired biopsy) for entry into this study. This consent is included in the main patient informed consent form.

Screening/baseline evaluations may be performed over more than 1 visit.

The timing of vital sign assessments should be such that it allows the blood draw (eg, PK blood sample) to occur at the timepoints indicated in Appendix A Table 2.

5.2 Treatment period

All procedures to be conducted during the treatment period will be performed according to the assessment schedule (see Appendix A Table 2).

Whenever vital signs and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: vital signs and then blood draws. The timing of the vital signs assessments should be such that it allows the blood draw (eg, PK blood sample) to occur at the timepoints indicated in Appendix A Table 2.

5.3 Follow-up period

Patients who are permanently discontinued from further receipt of IP, regardless of the reason, will be identified as having permanently discontinued treatment and will enter follow-up (see Appendix A Table 3).

Patients who permanently discontinue IP for reasons other than objective RECIST disease progression should continue to have RECIST scans performed at Week 8 ± 1 week, Week 12 ± 1 week, and then every 8 weeks ± 1 week (relative to the date of first dose) until confirmed objective disease progression/death (whichever comes first) as defined in Appendix A Table 3.

Following confirmed disease progression, patients should continue to be followed for survival.

All procedures to be conducted during the follow-up period will be performed according to the assessment schedule (see Appendix A Table 3).

Whenever vital signs, ECGs, and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: ECG, vital signs, and then blood draws. The timing of the first 2 assessments should be such that it allows the blood draw (eg, PK blood sample) to occur at the timepoints indicated in Appendix A Table 3. All patients will be followed for survival until the end of the study.

6. STUDY ASSESSMENTS

Please also refer to Section 6 of the master protocol for study assessments applicable to all arms of the study. Additional/specific study assessments applicable to Arm A are listed below.

6.1 Efficacy assessments

See Section 6.1 of the master protocol.

Efficacy in Arm A will be assessed on images collected at Week 8, Week 12, and then every 8 weeks ± 1 week until confirmed objective disease progression or off study. The Week 12 scan must be acquired no earlier than 4 weeks from the prior Week 8 scan.

It is important to follow the assessment schedule as closely as possible (Appendix A Table 2). If an unscheduled imaging assessment is performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at his or her next regularly scheduled imaging visit.

According to RECIST 1.1, objective tumor response (CR or PR) should be confirmed preferably at the next scheduled imaging visit and not less than 4 weeks after the visit when the response was last observed.

According to RECIST 1.1 modified for confirmation of progression, a confirmatory scan is required following an overall time point assessment of progression, preferably at the next scheduled imaging visit and no earlier than 4 weeks after the previous assessment of PD in the absence of clinically significant deterioration. Treatment will continue between the initial assessment of progression and confirmation for progression.

If a patient discontinues treatment (and/or receives a subsequent anticancer therapy) after the initial assessment of progression, then the patient should continue to be followed with scheduled imaging until confirmed objective disease progression.

Confirmation of progression guidelines are set for the following reasons:

- for patient management and treatment decisions
- in the absence of significant clinical deterioration, to promote the collection of additional scans after the first radiologic RECIST 1.1 assessment of progressive

disease (PD) in order to distinguish pseudoprogression from true radiologic progression, also known as RECIST 1.1 modified for confirmation of progression

Confirmed objective disease progression refers to either of the following scenarios: 1. clinical progression/deterioration followed by a radiologic verification scan (PD by RECIST 1.1); or 2. in the absence of significant clinical deterioration, radiologic PD by RECIST 1.1 followed by a second radiologic confirmation scan with PD assessed according to the specific confirmation of progression criteria listed below. RECIST 1.1 modified for confirmation of progression refers to the second scenario above. The confirmatory scan should occur preferably at the next scheduled imaging visit and no earlier than 4 weeks following the date of the immediate prior assessment of RECIST 1.1 PD.

Immediate prior radiologic progression would be considered confirmed if any the following criteria are met in the confirmatory scan:

- ≥20% increase in the sum diameters of target lesions (TLs) compared with the nadir at 2 consecutive visits, with an absolute increase of at least 5 mm in sum of diameters compared to nadir,

- and/or significant progression (worsening) of non-target lesions (NTLs) and/or of pre-existing new lesions at the confirmatory scan time-point compared with the immediate prior time-point (Note: Pre-existing new lesions are evaluated as NTLs at the confirmatory scan time-point),

- and/or additional new unequivocal lesions at the confirmatory scan time-point.

NOTE: In order to have confirmed objective disease progression, there should be two consecutive PD's, the first PD by RECIST 1.1 and the second PD using the confirmation of progression criteria (above). If the first PD by RECIST 1.1 is not confirmed, continue with assessments until the next PD by RECIST 1.1, which in turn will need its own immediate subsequent confirmation scan.

In the absence of significant clinical deterioration, treatment with study drug may continue between the initial assessment of progression and the scan to confirm progression.

If the confirmation scan confirms progression, then the date of the prior scan with PD should be declared as the date of progression.

If progression is not confirmed, in the absence of significant clinical deterioration, then the patient should continue study drug and on-treatment assessments until the next PD which will also require a follow-up confirmation scan. **If the first PD is not confirmed by the immediate next scan, then the Investigator should not change the PD assessment of the first scan.**

If a patient discontinues treatment (and/or receives a subsequent anticancer therapy) prior to radiologic progression, then the patient should still continue to be followed until confirmed objective disease progression.

6.2 Safety assessments

6.2.1 Laboratory safety assessments

The laboratory variables to be measured are presented in Table 4 (clinical chemistry), Table 5 (hematology), and Table 6 (urinalysis).

Other safety tests to be performed at screening include assessment for hepatitis B surface antigen, hepatitis C antibodies, and human immunodeficiency virus antibodies.

The following laboratory variables will be measured:

Appendix A Table 4 Laboratory - clinical chemistry

Albumin	Lipase[b]
Alkaline phosphatase[a]	Magnesium[c]
ALT[a]	Potassium
Amylase[b]	Sodium
AST[a]	Total bilirubin[a]
Bicarbonate[c]	Total protein
Calcium	TSH
Chloride[c]	T3 free[d] (reflex)
Creatinine clearance[c]	T4 free[d] (reflex)
Creatinine	Urea or blood urea nitrogen, depending on local practice
Gamma glutamyltransferase[c]	
Glucose	
Lactate dehydrogenase	

[a] Tests for ALT, AST, alkaline phosphatase, and total bilirubin must be conducted and assessed concurrently. If total bilirubin is >2 × upper limit of normal (and evidence of Gilbert's syndrome), then fractionate it into direct and indirect bilirubin.

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

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

[d] Free T3 and T4 will be measured in Arm A if TSH is abnormal or if there is a clinical suspicion of an AE related to the endocrine system.

AE Adverse event; ALT Alanine aminotransferase; AST Aspartate aminotransferase; T3 Triiodothyronine; T4 Thyroxine; TSH Thyroid-stimulating hormone.

Appendix A Table 5 Laboratory – hematology

Basophils	Monocytes
Eosinophils	Neutrophils
Hematocrit	Platelet count
Hemoglobin	Red blood cell count
Lymphocytes	Total while blood cell count
Mean corpuscular hemoglobin	Activated partial thromboplastin time
Mean corpuscular hemoglobin concentration	International Normalized Ratio
Mean corpuscular volume	Partial thromboplastin time

Note: For coagulation parameters, activated partial thromboplastin time, partial thromboplastin time and international normalized ratio are to be assessed at baseline and as clinically indicated.

Note: absolute values of blood cells should be provided where possible rather than percentages (e.g. for white cell differential counts)

Appendix A Table 6 Laboratory – urinalysis

Bilirubin	Ketones
Blood	pH
Color and appearance	Protein
Glucose	Specific gravity

Note: Urinalysis must be done at baseline and then as clinically indicated.

Note: Microscopy should be used as appropriate to investigate white blood cells and use the high power field for red blood cells.

6.2.2 Vital Signs

Vital signs (blood pressure [BP], pulse, temperature, and respiration rate) will be evaluated according to the assessment schedules (see Appendix A Table 2 and Appendix A Table 3). Body weight is also recorded at each visit along with vital signs.

On the first infusion day, patients in the durvalumab + tremelimumab combination therapy group will be monitored, and vital signs will be collected/recorded in the eCRF prior to, during, and after infusion of IP as presented in the bulleted list below:

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

- Prior to the beginning of the infusion (measured once from approximately 30 minutes before up to 0 minutes [ie, the beginning of the infusion])
- Approximately 30 minutes during the infusion (halfway through infusion)
- At the end of the infusion (approximately 60 minutes ± 5 minutes)
- If the infusion takes longer than 60 minutes, then BP and pulse measurements should follow the principles as described above or be taken more frequently if clinically indicated. A 1-hour observation period is recommended after the first infusion of durvalumab and tremelimumab.
- Subsequent infusions
- BP, pulse, and other vital signs should be measured and collected/recorded in the eCRF prior to the start of the infusion. Patients should be carefully monitored, and BP and other vital signs should be measured during and post infusion as per institution standard and as clinically indicated. Any clinically significant changes in vital signs should be entered onto an unscheduled vital signs case report form (CRF) page.

Situations in which vital signs results should be reported as AEs are described in Section 7.3.7. For any AEs of infusion reactions, please enter the vital signs values into the CRF.

6.2.3 Other Safety Assessments

If new or worsening pulmonary symptoms (eg, dyspnea) or radiological abnormality suggestive of pneumonitis/interstitial lung disease is observed, a full investigation is required, as described in detail in the Dosing Modification and Toxicity Management Guidelines (Section 7.5). If this is a potential risk for the specific arm then specific safety management guidelines will be applied. The results of the full diagnostic workup (including high-resolution computed tomography (HRCT), blood and sputum culture, haematological parameters etc) will be captured in the eCRF. It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of pneumonitis (ILD) should be considered and the Dosing Modification and Toxicity Management Guidelines should be followed.

Pneumonitis (ILD) investigation

The following assessments, and additional assessments if required, will be performed to enhance the investigation and diagnosis of potential cases of pneumonitis. The results of the assessment will be collected.

- Physical examination

  - Signs and symptoms (cough, shortness of breath and pyrexia, etc.) including auscultation for lung field will be assessed.

- SpO2
  - Saturation of peripheral oxygen (SpO2)

- Other items
  - When pneumonitis (ILD) is suspected during study treatment, the following markers should be measured where possible:

    (i) ILD Markers (KL-6, SP-D) and β-D-glucan

    (ii) Tumor markers: Particular tumor markers which are related to disease progression.

    (iii) Additional Clinical chemistry: CRP, LDH

6.3 Biomarker analysis

CCI

[redacted]

6.4 Pharmacokinetic and Immunogenicity analysis

Durvalumab and tremelimumab PK concentration data and summary statistics will be tabulated by treatment, analyte and timepoint. Individual and mean blood concentration-time profiles will be generated. No PK parameters will be determined due to sparse sampling.

Immunogenicity results will be analyzed descriptively by summarizing the number and percentage of patients who develop detectable ADAs against durvalumab and tremelimumab.

The immunogenicity titer and presence of neutralizing ADAs will be reported for samples confirmed positive for the presence of ADAs. The effect of immunogenicity on PK, efficacy, and safety will be evaluated, if the data allow.

6.5 Storage and destruction of pharmacokinetic/ADA samples

PK and ADA samples will be disposed of a maximum of 10 years after the end of this study

PK and ADA samples may be disposed of or destroyed and anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled PK samples to further evaluate and validate the analytical method. Results from such analyses may be reported separately from the Clinical Study Report (CSR).

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the CSR but separately in a Bioanalytical Validation Report.

Any residual back-up PK samples may be used for future exploratory biomarker research (in this case, residual back-up PK samples will be shipped to AstraZeneca Biobank; see details in the Laboratory Manual).

7. SAFETY REPORTING AND MEDICAL MANAGEMENT

Please refer to Section 7 of the master protocol for details of reporting of AEs, SAEs, AESIs, paternal exposure, and management of IP-related toxicities applicable to all arms in the study. Additional details for reporting of AEs, SAEs, AESIs, paternal exposure, and management of IP-related toxicities applicable to Arm A are described below.

7.1 Reporting of adverse events

New onset AEs and SAEs will be collected from the time of the patient signing signature of the informed consent form, throughout the treatment period, and including the follow-up period is completed (90 days after the last dose of durvalumab ±tremelimumbab). If an event that starts post the defined safety follow up period noted above, is considered to be due to a late onset toxicity to study drug, then it should be reported as an AE or SAE as applicable.

7.2 Reporting of serious adverse events

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

7.3 Pregnancy

7.3.1 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 180 days after the last dose of durvalumab + tremelimumab combination therapy or 90 days after the last dose of durvalumab monotherapy, whichever is the longer time period.

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose until 180 days after the last dose of durvalumab + tremelimumab combination therapy, or 90 days after the last dose of durvalumab monotherapy, whichever is the longer time period, should, if possible, be followed up and documented.

7.4 Overdose

Use of durvalumab or tremelimumab in doses in excess of that specified in the protocol is considered to be an overdose. There is currently no specific treatment in the event of overdose of durvalumab or tremelimumab, and possible symptoms of overdose are not established. See Section 7.6 of the master protocol.

7.5 Management of investigational product-related toxicities

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

- Treat each of the toxicities with maximum supportive care (including holding the agent suspected of causing the toxicity if required)
- If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of the assigned IP along with appropriate continued supportive care. If medically appropriate, dose modifications are permitted
- All dose modifications should be documented with clear reasoning and documentation of the approach taken
- If new or worsening pulmonary symptoms (e.g. dyspnoea) or radiological abnormality suggestive of pneumonitis/interstitial lung disease is observed, toxicity management as described in detail in the Toxicity Management Guidelines will be applied. The results of the full diagnostic workup (including high-resolution computed tomography (HRCT), blood and sputum culture, haematological parameters etc) will be captured in the eCRF. It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as

lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of pneumonitis (ILD) should be considered and the Toxicity Management Guidelines should be followed.

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

7.5.1 Durvalumab and durvalumab + tremelimumab

Patients should be thoroughly evaluated and appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. In the absence of a clear alternative etiology, events should be considered potentially immune related.

In addition, there are certain circumstances in which durvalumab and tremelimumab should be permanently discontinued (see Section 4.7 of the master protocol and the Toxicity Management Guidelines).

Following the first dose of IP, subsequent administration of durvalumab and tremelimumab can be modified based on toxicities observed as described in the Toxicity Management Guidelines. These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of his or her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to durvalumab monotherapy and the durvalumab + tremelimumab regimen by the reporting Investigator.

Dose reductions are not permitted. In case of doubt, the Investigator should consult with the Study Physician.

7.5.2 Toxicity Management Guidelines

Comprehensive toxicity management guidelines (TMG) have been developed to assist investigators with the recognition and management of toxicities associated with the use of the immune-checkpoint inhibitors durvalumab [MEDI4736] (PD-L1 inhibitor) and tremelimumab (CTLA-4 inhibitor). Given the similar underlying mechanisms of toxicities observed with these two compounds, these guidelines are applicable to the management of patients receiving either drug as monotherapy or in combination. Additionally, these guidelines are applicable when either drug is used alone or in combination and is administered concurrently or sequentially with other anti-cancer drugs (i.e. antineoplastic chemotherapy, targeted agents), as part of a protocol specific treatment regimen. The TMGs provide information for the management of immune-mediated reactions, infusion-related reactions, and non-immune mediated reactions that may be observed with checkpoint inhibitor monotherapy or combination checkpoint inhibitor regimens, with specific instructions for dose modifications (including discontinuations) and treatment interventions. Investigators are advised however to use local practice guidelines and consult local references for the management of toxicities observed with other cancer treatment. The most current version of the TMGs entitled “Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion-Related,

and Non-Immune Mediated Reactions (MEDI4736) Monotherapy or Combination Therapy with Tremelimumab or Tremelimumab Monotherapy" is provided to the investigative site as an Annex document and is maintained within the Site Master File. In addition, a version of the current Dosing Modification and Toxicity Management Guidelines is available through the following link: https://tmg.azirae.com. Please contact the clinical study associate for information on how to gain access to this website.

7.6 Adverse events of special interest

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the Investigational Product and may require close monitoring and rapid communication by the investigator to the sponsor. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this investigational product.

AESIs for durvalumab ± tremelimumab include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants, and/or hormone replacement therapy. These AESIs are being closely monitored in clinical studies with durvalumab monotherapy and combination therapy. An immune mediated adverse event (imAE) is defined as an AESI that is associated with drug exposure and is consistent with an immunemediated mechanism of action and where there is no clear alternate etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE.

If the Investigator has any questions in regard to an AE being an imAE, the Investigator should promptly contact the Study Physician.

AESI/imAEs observed with PD-L1/PD-1 agents such as durvalumab and durvalumab in combination with tremelimumab include:

- Pneumonitis
- Hepatitis
- Diarrhea/Colitis
- Intestinal perforations
- Endocrinopathies (ie, events of hypo- and hyper-thyroidism, adrenal insufficiency, hypophysitis/hypopituitarism and type I diabetes mellitus)
- Nephritis
- Rash/Dermatitis

- Myocarditis
- Myositis / Polymyositis
- Pancreatitis
- Rare/less frequent imAEs including neuromuscular toxicities such as myasthenia gravis and Guillain-Barré syndrome.

Other inflammatory responses that are rare / less frequent with a potential immune-mediated aetiology include, but are not limited to, pericarditis, sarcoidosis, uveitis and other events involving the eye, skin, haematological, rheumatological events, vasculitis, non-infectious meningitis and non-infectious encephalitis. It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs.

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

Further information on these risks (eg, presenting symptoms) can be found in the current version of the durvalumab and tremelimumab IBs. More specific guidelines for their evaluation and treatment are described in detail in the Dosing Modification and Toxicity Management Guidelines (see Section 7.5). These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of his or her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to the study drug/study regimen by the reporting Investigator.

7.6.1 Immune-related adverse events

Based on the mechanism of action of durvalumab and tremelimumab leading to T-cell activation and proliferation, there is a possibility of observing irAEs during the conduct of this study. Potential irAEs may be similar to those seen with the use of ipilimumab, BMS-936558 (antiPD-1 mAb), and BMS-936559 (anti-PD-L1 mAb-) and may include immune-mediated enterocolitis, dermatitis, hepatitis (hepatotoxicity), pneumonitis, and endocrinopathies (Hodi et al 2010, Brahmer et al 2012, Topalian et al 2012). These AEs are inflammatory in nature and can affect any organ. With anti-PD-L1 and anti-CTLA-4 combination therapy, the occurrence of overlapping or increasing cumulative toxicities that include irAEs could potentially occur at higher frequencies than with either durvalumab or tremelimumab monotherapy. Patients should be monitored for signs and symptoms of irAEs. In the absence of an alternate etiology (eg, infection or PD), an immune-related etiology should be considered for signs or symptoms of enterocolitis, dermatitis, pneumonitis, hepatitis, and endocrinopathy. In addition to the dose modification guidelines provided in Appendix A Table 7, it is recommended that irAEs are managed according to the general treatment guidelines outlined for ipilimumab (Weber et al 2012). These guidelines recommend the following:

1. Patients should be evaluated to identify any alternative etiology.

2. In the absence of a clear alternative etiology, all events of an inflammatory nature should be considered immune related.

3. Symptomatic and topical therapy should be considered for low-grade events.

4. Systemic corticosteroids should be considered for a persistent low-grade event or for a severe event.

5. More potent immunosuppressives should be considered for events not responding to systemic steroids (eg, infliximab or mycophenolate; see Appendix A Table 7).

If the Investigator has any questions in regard to an AE being an irAE, the Investigator should immediately contact the Study Physician.

8. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

8.1 Identity of investigational product(s)

Please see Section 8 of the master protocol for the general information on the IP. Additional IP information applicable to Arm A is described in this section.

Investigational product	Dosage form and strength
Durvalumab (MEDI4736)	50 mg/mL solution, IV
Tremelimumab	20 mg/mL solution, IV

8.1.1 Durvalumab

Durvalumab will be supplied by AstraZeneca as a 500-mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab (MEDI4736), CCI [redacted] The nominal fill volume is 10 mL. IP vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Drug product should be kept in secondary packaging until use to prevent excessive light exposure.

The dose of durvalumab (MEDI4736) for administration must be prepared by the Investigator's or site's designated IP manager using aseptic technique. Total time from needle puncture of the durvalumab (MEDI4736) vial to the start of administration should not exceed:

- 24 hours at 2°C to 8°C (36°F to 46°F)
- 4 hours at room temperature

Infusion solution must be allowed to equilibrate to room temperature prior to commencement of administration.

A dose of 1500mg (for patients >30kg in weight) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab (MEDI4736) concentration ranging from 1 to 20 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter. Add 30.0 mL of durvalumab (MEDI4736) (ie, 1500mg of durvalumab (MEDI4736)) to the IV bag. The IV bag size should be selected such that the final concentration is within 1 to 20 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

Weight-based dosing of 20 mg/kg (for patients ≤ 30 kg) will be a administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab (MEDI4736) concentration ranging from 1 to 20 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter.

Standard infusion time 1 hour. In the event that there are interruptions during infusion, the total allowed infusion time should not exceed 8 hours at room temperature.

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

The IV line will be flushed with a volume of IV diluent equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered and document if the line was not flushed.

If either preparation time or infusion time exceeds the time limits a new dose must be prepared from new vials. Durvalumab (MEDI4736) does not contain preservatives, and any unused portion must be discarded.

Preparations are to be in accordance with the study-specific drug handling instructions.

8.1.2 Tremelimumab

Tremelimumab will be supplied by AstraZeneca as a 400-mg vial solution for infusion after dilution. The solution contains 20 mg/mL tremelimumab, CCI [redacted] The nominal fill volume is 20.0 mL. IP vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Drug product should be kept in secondary container until use to prevent excessive light exposure.

All preparation details can be found in the IP Handling Instructions.

The dose of tremelimumab for administration must be prepared by the Investigator's or site's designated IP manager using aseptic technique. Total time from needle puncture of the tremelimumab vial to the start of administration should not exceed:

- 24 hours at 2°C to 8°C (36°F to 46°F)

- 4 hours at room temperature

Infusion solution must be allowed to equilibrate to room temperature prior to commencement of administration.

A dose of 75 mg (for patients >30kg in weight) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final tremelimumab concentration ranging from 0.10 to 10 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter. Add 3.8 mL (ie,75 mg of tremelimumab, with the dose volume rounded to the nearest tenth mL) to the IV bag. The IV bag size should be selected such that the final concentration is within 0.10 to 10 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

Weight-based dosing of 1 mg/kg (for patients ≤ 30 kg) will be a administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final tremelimumab concentration ranging from 0.10 to 10 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter.

Standard infusion time is 60 minutes (± 5 minutes). Less than 55 minutes is considered a deviation. In the event that there are interruptions during infusion, the total allowed infusion time should not exceed 8 hours at room temperature.

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

The IV line will be flushed with a volume of IV diluent equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered and document if the line was not flushed.

If either preparation time or infusion time exceeds the time limits a new dose must be prepared from new vials. Tremelimumab does not contain preservatives, and any unused portion must be discarded.

Tremelimumab will be administered first; the durvalumab infusion will start approximately 1 hour (maximum 2 hours) after the end of the tremelimumab infusion. Standard infusion time for each is 1 hour. In the event that there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature per infusion. If there are no clinically significant concerns after the first cycle, then, at the discretion of the Investigator, all other cycles of durvalumab can be given immediately after the tremelimumab infusion has finished.

8.2 Dose and treatment regimens

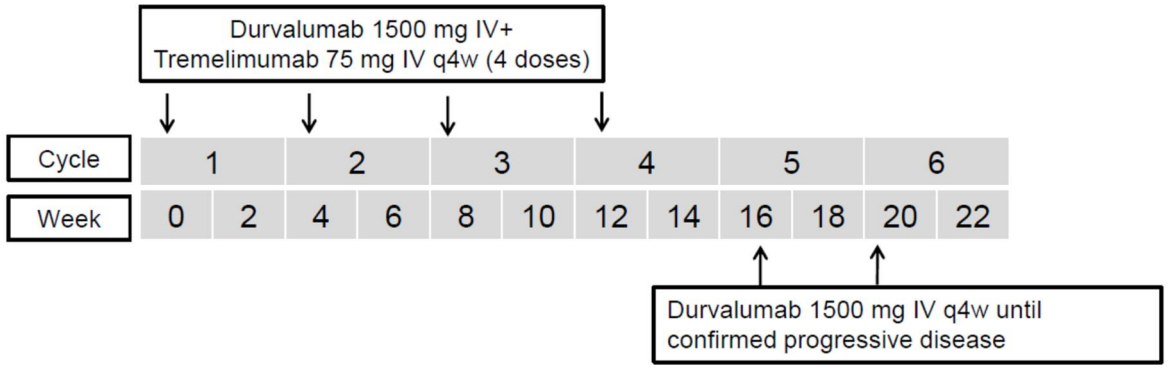
For Arm A, up to 20 eligible patients will be enrolled, and all patients will receive:

Durvalumab 1500 mg + tremelimumab 75 mg via IV infusion q4w, starting on Week 0, for up to a total of 4 cycles/doses followed by durvalumab monotherapy 1500 mg via IV infusion

q4w, starting after completion of the 4th cycle of combination treatment, until confirmed PD and Investigator confirmation that the patient is no longer receiving clinical benefit from the treatment, or for other discontinuation criteria. If a patient's weight falls to 30 kg or less the patient should receive weight-based after discussion between Investigator and Study Physician, until the weight improves to >30 kg, at which point the patient should start receiving the fixed dosing of durvalumab 1500mg and 75mg tremelimumab q4w (during the combination phase of treatment). The equivalent weight based doses to the fixed doses are 20 mg/kg of durvalumab and 1mg/kg tremelimumab q4w.

In the first cycle of durvalumab + tremelimumab treatment, tremelimumab will be administered first; the durvalumab infusion will start approximately 1 hour (maximum 2 hours) after the end of the tremelimumab infusion. If there are no clinically significant concerns after the first cycle, then, at the discretion of the Investigator, all other cycles of durvalumab can be given immediately after the tremelimumab infusion has finished.

Appendix A Figure 2 Durvalumab + tremelimumab combination therapy dosing schedule



IV Intravenous; q4w Every 4 weeks.

8.2.1 Duration of treatment and criteria for treatment through progression

All treatment will be administered beginning on Day 1 until confirmed PD unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. Treatment through progression will only be considered for arms containing durvalumab +/- tremelimumab.

Progression during treatment

During the treatment period patients may continue receiving therapy in the setting of unconfirmed radiologic progressive disease (PD) according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1), at the Investigator's discretion, until progression is confirmed. A confirmatory scan is required following a RECIST 1.1 overall time point assessment of progression (PD), preferably at the next scheduled visit and no earlier than 4

weeks after the previous assessment of PD. Patients with PD by RECIST 1.1 (unconfirmed and confirmed) who, in the Investigator's opinion, continue to receive benefit from their assigned treatment and who meet the criteria for treatment in the setting of PD may continue to receive their assigned treatment for as long as they are gaining clinical benefit. However, patients will not be permitted to continue immunotherapy if progression occurs after confirmed response (CR or PR as defined by RECIST 1.1) to immunotherapy treatment in the target lesions (regardless of the appearance of new lesions) i.e the response and progression events both occurred in the target lesions while receiving immunotherapy during the same treatment period.

Patients with rapid tumour progression or with symptomatic progression that requires urgent medical intervention (eg, central nervous system metastasis, respiratory failure due to tumor compression, spinal cord compression) will not be eligible for continuing durvalumab ± tremelimumab.

Patients in the durvalumab + tremelimumab combination therapy arm meeting the retreatment criteria below will follow the same treatment guidelines followed during the original treatment period, including the same dose and frequency of treatments and the same schedule of assessments (with the exception of the PK, ADA, tumor biopsies, biomarker samples and optional PGx assessments, which do not need to be collected a second time).

Patients who meet the criteria for retreatment may only receive retreatment once.

Patients receiving the durvalumab + tremelimumab combination therapy arm may undergo retreatment as described below:

Patients who complete the 4 dosing cycles of the combination of durvalumab and tremelimumab portion of the regimen (with clinical benefit per Investigator judgment), but subsequently have evidence of PD during the durvalumab monotherapy portion of the combination regimen, with or without confirmation according to RECIST 1.1, may restart treatment with the combination.

For all patients who are treated through progression and for patients who are restarting durvalumab + tremelimumab the Investigator should ensure that:

- The patient does not have any significant, unacceptable, or irreversible toxicities that indicate continuing treatment will not further benefit the patient
- There is absence of clinical symptoms or signs indicating clinically significant disease progression accompanied by a decline in WHO/ECOG performance status to >1
- There is absence of rapid disease progression or threat to vital organs or critical anatomical sites (eg, central nervous system metastasis, respiratory failure due to tumor compression, or spinal cord compression) requiring urgent alternative medical intervention.

- The patient still fulfills the eligibility criteria for this study with the exception of inclusion criteria numbers 4 and 7, and exclusion criteria number 19.

During the retreatment period, patients in the durvalumab + tremelimumab combination therapy group will resume durvalumab dosing at 1500mg q4w with 75 mg of tremelimumab q4w for 4 doses/cycles each. Patients will then continue with durvalumab monotherapy at 1500mg q4w, beginning at Week 16, 4 weeks after the last dose of combination therapy until disease progression.

Patients who AstraZeneca and the Investigator determine may not continue treatment after PD will be followed up for survival. Patients who have discontinued treatment due to toxicity or symptomatic deterioration, or who have commenced subsequent anticancer therapy, will be followed up until confirmed disease progression and for survival.

8.3 Labeling

Please refer to Section 8.3 of the master protocol for details regarding labeling applicable to all arms. Additional details regarding labeling applicable to Arm A are described below.

Label text prepared for durvalumab will show the product name as “MEDI4736” or “durvalumab (MEDI4736)” depending on the agreed product name used in the approved study master label document. All naming conventions are correct during this transitional period.

Label text prepared for tremelimumab will show the product name as “tremelimumab”.

8.4 Storage

Please see Section 8.4 of the master protocol.

8.5 Compliance

Please see Section 8.5 of the master protocol.

8.6 Accountability

Please see Section 8.6 of the master protocol.

8.7 Concomitant and other treatments

Please refer to Section 8.7 of the master protocol for details regarding concomitant and other treatments applicable to all arms. Details regarding concomitant and other treatments applicable to Arm A are described below.

Refer also to the Dosing Modification and Toxicity Management Guidelines in Appendix A Table 7.

Appendix A Table 7 Prohibited concomitant medications for Arm A

Prohibited medication/class of drug:	Usage
Any investigational anticancer therapy other than those under investigation in this study	Should not be given concomitantly
mAbs against CTLA-4, PD-1, or PD-L1	Should not be given concomitantly
Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study	Should not be given during the study. (Concurrent use of hormones for non-cancer-related conditions [eg, insulin for diabetes and hormone replacement therapy] is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable [eg, by local surgery or radiotherapy])
Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and TNF-α blockers	Should not be given concomitantly. (Use of immunosuppressive medications for the management of IP-related AEs or in patients with contrast allergies is acceptable). In addition, use of inhaled, topical, and intranasal corticosteroids is permitted.
Drugs with laxative properties and herbal or natural remedies for constipation	Should be used with caution through to 90 days after the last dose of tremelimumab during the study
Sunitinib	Should not be given concomitantly or through 90 days after the last dose of tremelimumab (acute renal failure has been reported with combination therapy of tremelimumab and sunitinib)
EGFR TKIs	Should not be given concomitantly Should be used with caution in the 90 days following the last dose of durvalumab Increased incidence of pneumonitis (with third generation EGFR TKIs) and increased incidence of transaminase increases (with first generation EGFR TKIs) have been reported when durvalumab has been given concomitantly.
Live attenuated vaccines	Should not be given through 30 days after the last dose of IP
Herbal and natural remedies which may have immune-modulating effects	Should not be given concomitantly unless agreed by the sponsor

AE Adverse event; CTLA-4 Cytotoxic T–lymphocyte-associated antigen 4; EGFR Epidermal growth factor receptor; IP Investigational product; mAb Monoclonal antibody; PD-1 Programmed cell death 1; PD-L1 Programmed cell death ligand 1; TKI tyrosine kinase inhibitor; TNF Tumor necrosis factor.

Appendix A Table 8 Rescue/supportive medication for Arm A

Rescue/supportive medication	Usage
Concomitant medications or treatments (eg, acetaminophen or diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care, except for those medications identified as "prohibited," as listed above	To be administered as prescribed by the Investigator
Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy to non-target lesions, etc])	Should be used, when necessary, for all patients
Inactivated viruses, such as those in the influenza vaccine	Permitted

8.8 Post Study Access to Study Treatment

Please see Section 8.8 of the master protocol.

9. STATISTICAL ANALYSES BY ASTRAZENECA

Please refer to Section 9 of the master protocol for details regarding statistical analyses applicable to all arms. Additional details regarding statistical analyses applicable to Arm A are described below.

CCI

CCI

9.2 Adverse events

AEs observed up to 90 days following discontinuation of study treatment or until the initiation of the first subsequent therapy following discontinuation of treatment (whichever occurs first) will be used for the reporting of AE summary tables. This will more accurately depict AEs attributable to study treatment only, as a number of AEs up to 90 days following discontinuation of the study agents are likely to be attributable to subsequent therapy.

9.3 Study and data management by AstraZeneca

Please refer to Section 10 of the master protocol for details of the management of the study and data.

10. ETHICAL AND REGULATORY REQUIREMENTS

Please refer to Section 11 of the master protocol for details regarding ethical and regulatory requirements.

APPENDIX B ARM B: AZD1775 + CARBOPLATIN SUB-PROTOCOL

1. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC	Area under the plasma drug concentration-time curve
AUC(0-∞)	Area under the plasma drug concentration-time curve time 0 to infinity
BCRP	Breast cancer resistance protein
BID	Twice daily
CBDP	Carboplatin
CIDP	Chronic inflammatory demyelinating polyneuropathy
$C_{max,ss}$	Maximum plasma concentration at steady state
CrCl	Creatinine clearance
CRF	Case report form (electronic/paper)
CTCAE	Common Terminology Criteria for Adverse Event
CYP	Cytochrome P450
DHEA	Dehydroepiandrosterone
DNA	Deoxyribonucleic acid
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
eCRF	Electronic case report form
ECOG	Eastern Cooperative Oncology Group
ED-SCLC	Extensive stage disease small-cell lung cancer

Abbreviation or special term	Explanation
5-FU	5-fluorouracil
FDA	Food and Drug Administration
GFR	Glomerular filtration rate
IB	Investigator's Brochure
IRB	Institutional Review Board
IP	Investigational product
IV	Intravenous
MATE	Multi-antimicrobial extrusion protein
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
p53	Tumor protein 53
P-gp	P glycoprotein
PD	Progressive disease
PFS	Progression-free survival
PO	By mouth
PK	Pharmacokinetic(s)
PR	Partial response
q3w	Every 3 weeks
q4w	Every 4 weeks
q6w	Every 6 weeks
q12w	Every 12 weeks
RECIST 1.1	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SD	Stable disease
SCLC	small cell lung cancer
ULN	Upper limit of normal

Abbreviation or special term	Explanation
WEE1	A nuclear kinase belonging to the Ser/Thr family of protein kinases in the fission yeast Schizosaccharomyces pombe (S.◦pombe).
WoCBP	Women of childbearing potential

2. INTRODUCTION

2.1 Background and rationale for conducting this study

Study D419QC00002 is an open-label, multicenter, multi-arm, Phase II study in patients with extensive-stage small cell lung cancer (ED-SCLC) who have refractory or resistant disease, defined as patients who progress during first-line platinum based chemotherapy or those who progress within 90 days after completing first-line platinum based chemotherapy. Study D419QC00002 is modular in design, allowing evaluation of the safety, tolerability, pharmacokinetics (PK) and anti-tumor activity of different combinations of novel anti-cancer agents in patients with refractory or resistant ED-SCLC, and will consist of a number of study arms, each evaluating the safety and tolerability of a specific combination.

Arm B in Study D419QC00002 investigates the efficacy, safety, and tolerability of treatment with oral AZD1775 (PO) in combination with intravenous (IV) carboplatin (CBDP) in ED-SCLC patients.

The rationale for conducting this study is in Section 2.2 of the master protocol.

2.2 AZD1775

AZD1775 is a highly selective, ATP competitive, small-molecule inhibitor of the WEE1 kinase that sensitises tumour cells to cytotoxic agents and is being developed for the treatment of patients with advanced solid tumours with genetic deficiencies in DNA repair mechanisms. Inhibition of the DNA damage checkpoint kinase WEE1 potentiates genotoxic chemotherapies by abrogating cell-cycle arrest and eliminating the opportunity for proper DNA repair to occur. From a therapeutic standpoint, inhibition of checkpoint kinases that mediate cell-cycle arrest may force tumor cells to continue cell division before chemically induced DNA damage is repaired, eventually causing apoptosis or mitotic catastrophe (Medema and Macurek 2012).

In *in vitro* studies, AZD1775 inhibits WEE1 activity and induces DNA damage as well as G2 checkpoint escape in cell-based assays. AZD1775 increases cytotoxicity when used in combination with other DNA damaging agents, such as gemcitabine (GEMZAR®), cisplatin (Platinol®), and topotecan (HYCAMTIN®) in tumor protein 53 (p53)-deficient cell lines. In *in vivo* studies, AZD1775 was well tolerated and showed enhancement of anti-tumor efficacy by gemcitabine, CBDP, cisplatin, 5-fluorouracil (5-FU), and capecitabine (XELODA®) in nude rat xenograft tumor models. Similarly, in nude mouse xenograft models, AZD1775 treatment resulted in significant tumor growth inhibition at tolerated doses, and also enhanced the anti-tumor growth effect of gemcitabine, CBDP, and radiation therapy (see most recent AZD1775 Investigator's Brochure [IB]).
Small cell lung cancers (SCLCs) harbor multiple genomic alterations involved in cell cycle regulation, oncogenic signaling, and double-strand break repair. The most common genetic alterations in SCLC occur in: pTP53 (90%), retinoblastoma 1 (RBI, 85%) [Byers et al 2012], MYC (cMYC, MYCN, and MYCL1 - ~5% each), RAS (2%), and BRCA1/2 (3%). These alterations, and in particular, combinations of these alterations, force cancer cells to depend on

the G2-M checkpoint for restoring cell cycle function and division. It is estimated that 18% of SCLCs harbor mutations in cell cycle regulation (TP53) and in oncogenic signalling (MYC or RAS). Likewise, 3% of SCLCs harbor mutations in both cell cycle regulation (TP53) and DSB repair (BRCA1/2).

The high unmet medical need and prevalence of somatic alterations affecting cell cycle control and DNA repair make SCLC an important cancer setting to investigate AZD1775.

2.3 Carboplatin

CBDP is a second-generation platinum containing chemotherapeutic compound, and an analog of cisplatin. While cisplatin has two chloride groups, CBDP possesses a cyclobutane dicarboxylate (CBDCA) moiety. This results in lower reactivity and DNA binding kinetics, though the same platinum-DNA adducts are formed as those induced by cisplatin. CBDP however demonstrates less nephrotoxicity and neurotoxicity, and is less emetogenic than its parent compound cisplatin.

CBDP and etoposide (ETOPOPHOS®) or cisplatin and etoposide are the most commonly used chemotherapy regimen in the treatment of SCLC; CBDP is used more often than cisplatin in order to reduce the risk of emesis, neuropathy, and nephropathy (NCCN 2015).

2.4 Rationale for study design, doses, and control groups

The rationale for the unmet medical need in refractory or resistant ED-SCLC is described in Section 2.2.1 of the master protocol. The rationale for the specific study design aspects of Arm B is described below.

2.4.1 AZD1775 in combination with CBDP

Tumor cells rely on cell cycle checkpoints for repair of DNA damage induced by cytotoxic agents. As AZD1775 selectively inhibits WEE1, it effectively disrupts the regulation of cell cycle checkpoints, particularly the G2 checkpoint. Because cell cycle checkpoints are critical in the DNA damage response, AZD1775 can potentiate the activity of cytotoxic agents and thus acts to sensitize the tumor cell to the cytotoxic agent. Non-clinical studies have demonstrated that WEE1 effectively sensitizes tumor cells to cytotoxic effects of gemcitabine, cisplatin, or CBDP (refer to most recent AZD1775 IB). This has also been demonstrated clinically in platinum refractory ovarian cancer with objective response rate (ORR) as high as 41% (Leijen et al 2015).

2.4.2 Clinical experience with AZD1775

AZD1775 has been investigated in 12 AstraZeneca-sponsored or CCI [redacted] clinical studies, 6 of which are ongoing. As of 11 November 2015, a total of approximately 443 patients have been exposed to AZD1775 in AstraZeneca-sponsored or CCI [redacted] clinical studies. In addition, approximately 200 patients have also received AZD1775 as part of externally-sponsored scientific research. These patients have received single doses per cycle as high as 1300 mg of AZD1775 as monotherapy, 325 mg of AZD1775 in a single-dose in combination with chemotherapy, and 325 mg twice daily (BID) in a multiple-dose regimen

in combination with chemotherapy. For details on those studies, and for complete summary of the clinical safety and efficacy profile of AZD1775, refer to the current IB.

The most common adverse events (AEs) observed in studies of AZD1775 combined with chemotherapy include blood and lymphatic disorders, (ie, thrombocytopenia, neutropenia, leukopenia, anemia, and febrile neutropenia), gastrointestinal disorders (ie, diarrhea, vomiting, nausea, abdominal pain, and constipation), and blood investigations (ie, hematology and serum chemistries). Other reported safety concerns include electrocardiogram (ECG) QT prolongation, fatigue, influenza-like illness, malaise, mucosal inflammation, myalgia, palpitations, pruritus, pyrexia, rash, rash maculopapular, skin lesion, stomatitis, tachycardia, and loss of weight.

The single-dose maximum tolerated dose (MTD) for both the gemcitabine and cisplatin combination therapies was 200 mg of AZD1775 in this study (NCT00648648). Dose-limiting toxicities (DLTs) tended to be hematological in nature in the gemcitabine group and constitutional in the cisplatin group. The single-dose MTD for the combination with CBDP was 325 mg of AZD1775. DLTs in this group were related to serum chemistry.

DLTs observed in the multiple-dose CBDP combination have been both hematological and constitutional in nature. The multiple-dose MTD in combination with CBDP is AZD1775 225 mg BID × 5 for 2.5 days. Hematologic DLTs were most commonly observed in the multiple-dose AZD1775 combination treatment groups with gemcitabine and cisplatin. A MTD of AZD1775 in combination with gemcitabine was established with an interim dose of 50 mg BID on Day 1, 25 mg BID on Day 2, and 25 mg on Day 3. An attenuated once daily (QD) for 2-day schedule in combination with gemcitabine was invesitgated. Two DLTs (Grade 3 febrile neutropenia and Grade 3 aspartate aminotransferase and alanine aminotransferase (AST/ALT) increase) were observed at 200 mg QD for 2 days with the regimen in combination with gemcitabine. The dose was adjusted to 175 mg QD for 2 days and was determined to be the MTD. The MTD for combination with cisplatin has been exceeded at the 250 mg dose level, and tolerability of the MTD at 200 mg BID × 5 for 2.5 days has been confirmed.

The MTD for AZD1775 in combination with 5-FU was not reached due to early study termination. DLTs of encephalopathy and hyponatremia were observed in the AZD1775 20 mg BID in combination with 1000 mg/m^2 5-FU treatment group.

Triplet-based therapy of AZD1775, CBDP, and paclitaxel was administered in study NCT01357161: a Phase II study evaluating AZD1775 combined with CBDP and paclitaxel (ABRAXANE®) in patients with platinum-sensitive p53-mutant ovarian cancer. The starting dose of 225 mg AZD1775 (BID for 5 total doses) in Part 1 (an open-label dose escalation/ de-escalation study that employed a toxicity probability design to evaluate the safety and tolerability of the triplet combination) was generally well-tolerated. One patient experienced a DLT in the first 6 patients treated, and the dose remained at 225 mg BID for 2.5 days. A total of 15 patients were treated with 3 DLTs being reported (Grade 3 and 4 febrile neutropenia and Grade 4 thrombocytopenia). Other toxicities were generally blood and lymphatic system disorders and gastrointestinal disorders. Of the 14 evaluable patients by

Response Evaluation Criteria in Solid Tumors (RECIST 1.1) in Part 1, there were 11 PRs (6 confirmed and 5 unconfirmed), and 3 stable diseases (SDs); 7 patients were evaluable by CA-125 with 3 CRs and 4 PRs. All patients were treated at the 225 mg AZD1775 BID 2.5 day dose level in combination with paclitaxel and CBDP. The dose established in Part 1 was determined to be the recommended Phase II dose. Part 2 of the study compared the administration of AZD1775 at the recommended Phase II dose versus placebo in combination with CBDP AUC 5 and paclitaxel 175 mg/m2 in a double-blind fashion. Part 2 of the study is completed and showed the below final safety and efficacy data summary. As of 11 November 2015, a total of 59 patients were treated in the AZD1775 combination with paclitaxel and CBDP arm, and the following grade ≥3 AEs were reported: 21 (35.6%) neutropenia, 12 (20.3%) anemia, 12 (20.3%) thrombocytopenia, 6 (10.2%) diarrhea, 6 (10.2%) vomiting, and 3 (5.1%) nausea; compared to placebo and CBDP arm (n=60) with the following grade ≥3 AEs reported: 20 (33.3%) neutropenia, 7 (11.7%) thrombocytopenia, 4 (6.7%) anemia, 2 (3.3%) diarrhea, 2 (3.3%) alopecia, 1 (1.7%) nausea, and 1 (1.7%) vomiting.

For enhanced RECIST, median progression-free survival (PFS) for patients receiving AZD1775 plus chemotherapy was 34.14 weeks compared to 31.86 weeks for those receiving chemotherapy alone (hazard ratio 0.63 80% CI [0.45,0.89], p=0.080) [Oza et al 2015].
The combination of AZD1775 with topotecan and cisplatin in adult patients with cervical cancer (study NCT01076400) was evaluated. Toxicities were generally hematological and gastrointestinal in nature. No unexpected toxicities were observed.

Available preliminary efficacy data are encouraging, with confirmed partial responses (PRs) in patients participating in the 2 ovarian cancer trials, as well as the first time in human (FTIM) Phase I trial in solid tumors. Several studies are ongoing (AZD1775 IB).

2.4.3 Pharmacokinetic and pharmacodynamic data

The PK data of AZD1775 following a single oral administration showed a moderate rate of absorption with a maximum plasma drug concentration at steady state (C_{max}) occurring at 3 to 4 hours. Post-peak plasma concentrations declined essentially in a mono-exponential manner with a half-life in the region of 10 hours. Exposure as measured by C_{max} and area under the curve $AUC_{(0-\infty)}$ increased in a dose-proportional manner over the dose range of 325 to 1300 mg. Following single (100 to 325 mg) and multiple dose administrations of AZD1775 (25 to 325 mg BID and 100 to 200 mg QD) with CBDP, cisplatin, and gemcitabine, plasma exposure of AZD1775 was consistent with predictions based on the single-dose regimen. Preliminary investigation of drug-drug interactions (DDI) in the FTIM study (NCT00648648) suggests a 40% to 60% increase in the exposure of AZD1775 in the presence of aprepitant (moderate CYP3A4 inhibitor), but no effect with the concomitant administration of steroids (moderate CYP3A4 inducers). Preliminary studies also suggested that the Premarketed Oral Formulation (PMF) of AZD1775 was similar to that of the Fit-For-Purpose (FFP) formulation. Based on the preliminary comparison of the results of AZD1775 PK parameters at the 225 mg dose, PK estimates in Asian patients were 30% to 45% higher than in Western patients.

Pharmacodynamic analyses have mainly focused on CDK-1. By inhibiting WEE1, AZD1775 reduces phosphorylated CDK-1 levels relative to total CDK-1 with 125 mg BID of AZD1775 expected to be the threshold dose for target engagement.

Further information on the PK, metabolism, and pharmacodynamics effects of AZD1775 is provided in the current version of the AZD1775 IB.

2.4.4 CCI

CCI

[redacted]

2.4.5 Rationale for study endpoints

The rationale for study endpoints is provided in Section 2.2.3 of the master protocol.

2.5 Benefit/risk and ethical assessment

The unmet need in refractory or resistant ED-SCLC is described in Sections 2.1 and 2.3 of the master protocol. Additional information on the potential benefits of each agent (AZD1775 and CBDP) and an assessment of the potential and known risks can also be found in the current AZD1775 IB and in the manufacturer's label for CBDP (Food and Drug Administration 2014). Specific information relating to AZD1775 and CBDP is summarized below.

2.5.1 Potential benefits

2.5.1.1 AZD1775

AZD1775 has shown some clinical activity as monotherapy. Data is limited to 12 evaluable subjects from a Phase Ib study in advanced solid tumors (NCT02482311); CCI [redacted] In Part 1 of this study, confirmed PRs were observed in 2 patients carrying BRCA mutations: 1 with head and neck cancer and 1 with ovarian cancer. (Do et al, JCO, 2015)

2.5.1.2 CBDP

CBDP is registered for the treatment of ovarian cancer as monotherapy or in combination therapy for recurrent disease. CBDP is also used in the treatment of cancer of the lungs, testis, head and neck, and neuroblastoma. Additionally, CBDP in combination with etoposide is the standard first-line chemotherapeutic treatment of ED-SCLC (NCCN 2015).

2.5.1.3 AZD1775 + CBDP

AZD1775 in multiple-dose combination with CBDP: 44 out of 46 patients (CCI %) were evaluable for response. There was no confirmed PR observed in any of the evaluable patients. CCI [redacted] The most promising data comes from the recent Phase II study of AZD1775 + CBDP in patients with CCI [redacted] The median PFS was CCI [redacted] months (Leijen et al 2015).

2.5.2 Identified and potential risks

2.5.2.1 AZD1775

No AZD1775 monotherapy studies have been completed, and there are limited data available on the administration of AZD1775 as a monotherapy. It has therefore not been possible to reliably estimate the frequency of occurrence of expected AEs and laboratory abnormalities for AZD1775 monotherapy**.**

Please refer to Section 5.4 'emerging safety profile'of the current AZD1775 IB for complete list of events considered as identified risks, and Section 6 of IB 'summary of data and guidance to investigators' for information on the potential risks and risk mitigation strategy.

2.5.2.2 CBDP

Side effects of CBDP mainly consist of myelosuppression; especially thrombocytopenia, and leukopenia, nausea and vomiting, nephrotoxicity, liver toxicity (especially increased alkaline

phosphatase), ototoxicity and tinnitus, allergic reactions, neurotoxicity, alopecia, taste alterations, fever, and conjunctivitis.

2.5.2.3 AZD1775 + CBDP

The most common CCI [redacted]

Preliminary PK analyses revealed that co-administration of CCI [redacted]

2.5.3 Summary benefit: risk statement

The safety profile of AZD1775 when combined with CBDP has been shown to be acceptable, and AZD1775 has shown activity in several tumor types in the clinical development program to date. The potential benefit of this combination in ED-SCLC is unknown. Overall risks and benefits support the investigation of oral AZD1775 and carboplatin in patients with platinum refractory ED-SCLC according to this clinical protocol.

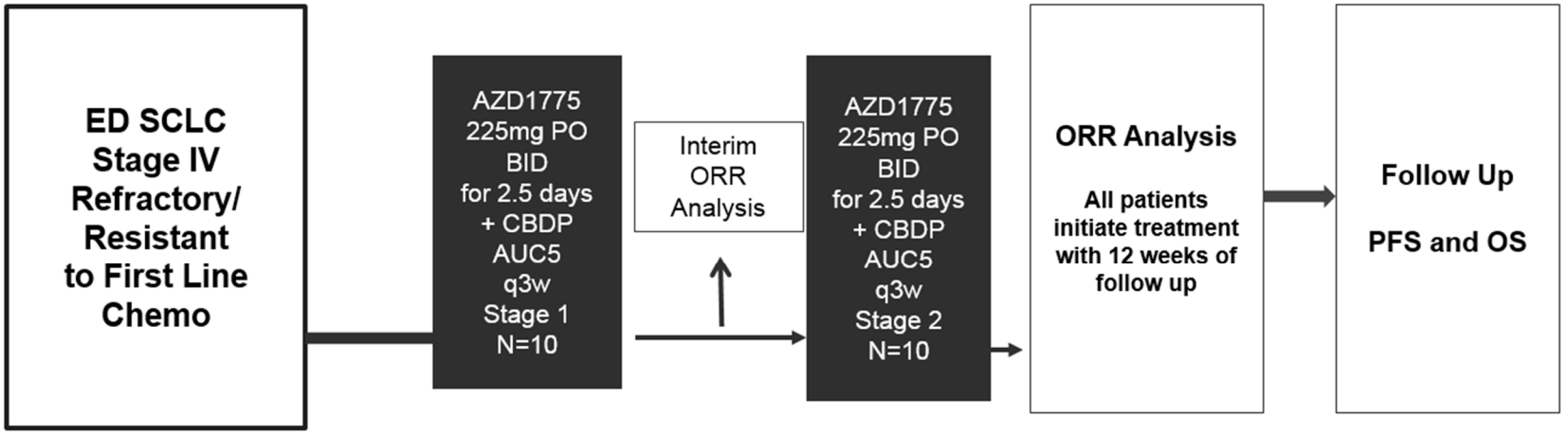
2.6 Study design

Arm B will investigate the preliminary efficacy, safety, and tolerability of AZD1775 (given PO) in combination with CBDP (given IV) to patients who progress during first-line chemotherapy (platinum refractory) or those who progress within 90 days after completing first-line chemotherapy (platinum resistant).

For Arm B, up to 20 eligible patients will be enrolled, and all patients will receive:

- AZD1775 225 mg BID PO for 2.5 days from Day 1 + CBDP AUC 5 Day 1 IV; every 3 weeks (q3w)

Appendix B Figure 1 Study design



BID Twice daily; CBDP Carboplatin; ED-SCLC Extensive-stage disease small-cell lung cancer; ORR Objective response rate; OS Overall survival; PFS Progression-free survival; PO By mouth; q3w Every 3 weeks.

3. STUDY OBJECTIVES

3.1 Primary objective

See Section 3.1 of the master protocol.

3.2 Secondary objectives

See Section 3.2 of the master protocol.

3.3 Safety objectives

See Section 3.3 of the master protocol.

3.4 Exploratory objectives

See Section 3.4 of the master protocol.

4. PATIENT SELECTION, ENROLLMENT, RANDOMIZATION, RESTRICTIONS, DISCONTINUATION, AND WITHDRAWAL

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

4.1 Inclusion criteria

1. Male or female ≥18 years at the time of screening.

2. Written informed consent and any locally required authorization (eg, Health Insurance Portability and Accountability Act in the US, EU Data Privacy Directive in the EU) obtained from the patient/legal representative prior to performing any protocol-related procedures, including screening evaluations.

3. Histologically or cytologically documented extensive disease American Joint Committee on Cancer Stage IV SCLC (T any, N any, M1 a/b) at initial diagnosis, also including patients with:

    - T3-4 due to multiple lung nodules that are too extensive or have tumor/nodal volume that is too large to be encompassed in a tolerable radiation plan.
    - Biopsy-proven mixed SCLC and NSCLC histology
    - Brain metastases; must be asymptomatic or treated and stable off steroids and anti-convulsants for at least 1 month prior to study treatment. Patients with suspected brain metastases at screening should have a computed tomography (CT)/magnetic resonance imaging (MRI) of the brain prior to study entry.

4. Patients must have demonstrated progressive disease (PD) either during first-line platinum-based chemotherapy (platinum refractory) or within 90 days of completing platinum-based chemotherapy (platinum resistant), and have not received further treatment apart from first-line platinum-based chemotherapy. Patients should be enrolled within 90 days of progression in order to be accepted into the study.

5. World Health Organization (WHO)/Eastern Cooperative Oncology Group (ECOG) Performance Status of 01 at enrolment- (see Section 6.3.1 of master protocol for ECOG assessment parameters)

6. At least 1 lesion, not previously irradiated, that can be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes, which must have a short axis ≥15 mm) with CT or MRI and that is suitable for accurate repeated measurements as per RECIST 1.1 guidelines.

7. Able and willing to swallow oral medication

8. Willingness and ability to comply with study and follow-up procedures.

9. Life expectancy of at least 8 weeks.

10. Adequate organ and marrow function as defined below;

    - Hemoglobin ≥9 g/dL
    - Absolute neutrophil count ≥1500/µL (use of granulocyte-colony stimulating factor is permitted)
    - Platelets ≥100000/µL

- ALT and AST ≤3 × upper limit of normal (ULN) or ≤5 × ULN if known hepatic metastases

- Serum bilirubin within normal limits (WNL) or ≤1.5 × the ULN in patients with liver metastases; or total bilirubin ≤3.0 × ULN with direct bilirubin WNL in patients with well documented Gilbert's syndrome

- Serum creatinine ≤1.5 × the ULN, or a calculated creatinine clearance (CrCl) ≥45 mL/min by the Cockcroft-Gault method:

$$\text{CrCl (glomerular filtration rate [GFR])} = \frac{(140 - \text{age}) \times (\text{weight/kg}) \times F^{a}}{(72 \times \text{serum creatinine mg/dL})}$$

[a] where F= 0.85 for females and F=1 for males

11. Evidence of post-menopausal status or negative urinary or serum pregnancy test for female pre-menopausal patients. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

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

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

    Females of childbearing potential should agree to use adequate contraceptive measures from 2 weeks prior to the study and until 6 months after study treatment discontinuation.

12. Male patients who are willing to use barrier contraception (ie, condoms) for the duration of the study and for 3 months after study treatment discontinuation.

4.2 Exclusion criteria

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

2. Previous enrollment in the present study.

3. Participation in another clinical study with an investigational product (IP) during the last 4 weeks.

4. Concurrent enrollment in another clinical study unless it is an observational (non-interventional) clinical study or the follow-up period of an interventional study.

5. Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of IP. Note: Local surgery of isolated lesions for palliative intent is acceptable where this does not affect assessment of target lesions.

6. Any condition that, in the opinion of the Investigator, would interfere with the evaluation of the IP or interpretation of patient safety or study results, including but not limited to ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs from the study medications, or compromise the ability of the patient to give written informed consent.

7. Radiation therapy to the chest and whole-brain irradiation must be completed at least 4 weeks prior to start of study treatment, and patients must have recovered from any acute adverse effects prior to start of study treatment. An exception to this is palliative radiotherapy for bone lesions and must be completed before the first dose of study treatment.

8. Past medical history of interstitial lung disease, drug-induced pneumonitis, radiation pneumonitis that required steroid treatment, or any evidence of clinically active interstitial lung disease.

9. Patient has an inability to swallow oral medications. Note: Patient may not have a percutaneous endoscopic gastrostomy tube or be receiving total parenteral nutrition.

10. Prior exposure to any WEE1 inhibitors.

11. Any known hypersensitivity or contraindication to the components of the study drugs, AZD1775 and CBDP, or drugs with a similar chemical structure or class to the study drugs.

12. History of hypersensitivity to active or inactive excipients of any investigational drug in the study those investigated in the study.

13. Patient has had prescription or non-prescription drugs or other products known to be sensitive to cytochrome P450 (CYP)3A4 substrates or CYP3A4 substrates with a narrow therapeutic index, or to be moderate to strong inhibitors/inducers of CYP3A4 which cannot be discontinued 2 weeks prior to the first day of study drug dosing and withheld throughout the study until 2 weeks after the last dose of study drug. Coadministration of aprepitant or fosaprepitant during this study is prohibited. The use of sensitive substrates of CYP3A4, such as atorvastatin, simvastatin and lovastatin, is also prohibited in this study. As grapefruit and Seville oranges are known to contain moderate inhibitors of CYP3A4, these fruits or their products (including marmalade, juice, etc.) should be avoided while taking AZD1775. (see Appendix I Disallowed Medications and Medications to ne Administered with Caution). Transporter studies (in vitro) have shown that AZD1775 is an inhibitor of breast cancer resistance protein (BRCP). The use of rosuvastatin in this study is prohibited.

14. Herbal preparations are not allowed throughout the study. These herbal medications include but are not limited to: St. John's wort, kava, ephedra (ma hung), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto and ginseng. Patients should stop using these herbal medications 7 days prior to first dose of study treatment.

15. Patients with Grade ≥2 neuropathy will be evaluated on a case-by-case basis after consultation with AstraZeneca Study Physician.

16. Patient with mean resting corrected QT interval (specifically QTc calculated using the Fridericia formula) > 470 msec from 3 ECGs performed within 5 minutes apart at study entry or congenital long QT syndrome.

17. Any of the following cardiac diseases currently or within the last 6 months as defined by New York Heart Association ≥ Class 2 (Appendix B1 New York Heart Association Criteria

18.).

- Unstable angina pectoris
- Congestive heart failure
- Acute myocardial infarction
- Conduction abnormality not controlled with pacemaker or medication
- Significant ventricular or supraventricular arrhythmias (patients with chronic rate-controlled atrial fibrillation in the absence of other cardiac abnormalities are eligible)

18. AZD1775 should not be given to patients who have a history of Torsades de pointes unless all risk factors that contributed to Torsades have been corrected (see Section

4.5.2AZD1775 has not been studied in patients with ventricular arrhythmias or recent myocardial infarction.

19. History of another primary malignancy except for:
    - Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of study drug and of low potential risk for recurrence
    - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
    - Adequately treated carcinoma in situ without evidence of disease (eg, cervical cancer in situ)
20. History of leptomeningeal carcinomatosis.
21. Spinal cord compression unless asymptomatic or treated and stable off steroids and anti-convulsants for at least 1 month prior to study treatment.
22. Female patients who are pregnant or breastfeeding.

4.3Patient enrollment and randomization

See Section 4.3 of the master protocol.

4.3.1 Procedures for handling incorrectly enrolled or randomized patients

See Section 4.4 of the master protocol.

4.4 Methods for assigning treatment groups

Not Applicable.

4.5 Restrictions

Please refer to Section 4.6 of the master protocol for details of the restrictions that apply to all patients in the study. Restrictions specific to Arm B include:

AZD1775 should be taken with 8 ounces of water approximately 2 hours before or 2 hours after food.

If BID dosing and a patient misses one of the two daily doses according to schedule, the dose should be taken as soon as possible, but not more than 6 hours after the missed dose was scheduled. If greater than 6 hours, the missed dose should be skipped and the patient should take the next dose when scheduled.

If vomiting occurs after a patient takes the AZD1775 dose, the patient should be instructed not to retake the dose, but to wait until the next scheduled dose of AZD1775. If no dose is scheduled for the following day, the dose will not be 'made up'. If vomiting persists, the patient should contact the Investigator.

4.5.1 Women of childbearing potential

Women of childbearing potential (WoCBP) may be included only if acceptable contraception is in place for 2 weeks before commencing study treatment, for the duration of the study, and for 6 months after the last dose of study drug.

WoCBP is defined as women between menarche and menopause who have not been permanently or surgically sterilized and are capable of procreation.

All WoCBP must have a negative pregnancy test during screening and within 3 days prior to starting each treatment cycle.

Male patients who are involved in the study must agree to avoid procreative and unprotected sex (ie, using acceptable forms of contraception as described in Appendix G) and must not donate sperm during the study and for 6 months after the last dose of study drug. Where the female partner is pregnant or not using effective birth control, men should be advised to abstain while in the study and for 6 months after the last dose of study drug.

Female partners, who are of childbearing potential, of men participating in the study will also be required to use effective contraceptive measures (detailed in Appendix G) while their partner is on study drug and for 6 months thereafter.

Because of the possibility of irreversible infertility due to therapy with carboplatin, male patients will be advised to arrange for the freezing of sperm samples prior to the start of the study should they wish to father children at a future date.

4.5.2 Patients with a history of Torsades de pointes

AZD1775 should not be given to patients who have a history of Torsades de pointes unless all risk factors that contributed to Torsades have been corrected. AZD1775 has not been studied in patients with ventricular arrhythmias or recent myocardial infarction. See appendix I for a list of drugs that can cause Torsades de pointes.

4.6 Discontinuation of investigational product

See Section 4.9 of the master protocol.

4.7 Criteria for withdrawal

See Section 4.10 of the master protocol.

4.8 Discontinuation of the study

See Section 4.11 of the master protocol.

5. STUDY PLAN AND TIMING OF PROCEDURES

The procedures for the screening and the treatment periods in this study are presented in Appendix B Table 1.

Appendix B Table 1 Schedule of assessments for AZD1775 + Carboplatin combination therapy

		AZD1775 and Carboplatin (cycle 21 days)									FOLLOW UP		For details see
	Screening	**Cycle 1**				**Cycle 2**		**Cycle 3 and beyond**			**End of study treatment visit (30 days FU) ± 2 days**	**Every 2 months (± 2 weeks)**	
Assesment	**Baseline (-28 to -1)**	**Day 1**	**Day 3**	**Day 8**	**Day 15**	**Day 1 (± 2 days)**	**Day 8 (± 2 days)**	**Day 1 (± 2 days)**	**Day 3**	**Day 8 (± 2 days)**			
Informed consent: study procedures including biomarker sample collection [a]	X												Section 6 of the master protocol
Study Procedures													
Physical examination (full)	X	X				X		X			X		Section 6.2.2 of master protocol
Vital signs[b]	X	X				X		X			X		Section 6.2.4 of master sprotocol
ECG[c]	X	X				X		X					Section 6.2.3 of master protocol
Concomitant medications	X	X				X		X			X		Section 8.7 of master protocol

Appendix B Table 1 Schedule of assessments for AZD1775 + Carboplatin combination therapy

		AZD1775 and Carboplatin (cycle 21 days)									FOLLOW UP		For details see
	Screening	**Cycle 1**				**Cycle 2**		**Cycle 3 and beyond**			**End of study treatment visit (30 days FU) ± 2 days**	**Every 2 months (± 2 weeks)**	
Assesment	**Baseline (-28 to -1)**	**Day 1**	**Day 3**	**Day 8**	**Day 15**	**Day 1 (± 2 days)**	**Day 8 (± 2 days)**	**Day 1 (± 2 days)**	**Day 3**	**Day 8 (± 2 days)**			
Demography, including baseline characteristics and tobacco use	X												Section 6 of master protocol
Eligibility criteria	X												Sections 4.1 and 4.2 of master protocol and Appendix B sections 5.1 and 5.2
Laboratory assesments													
Clinical chemistry	X	X[d]		X	X	X	X	X		X	X		Table 2 Appendix B
Hematology	X	X[d]		X	X	X[e]	X	X[e]		X	X		Table 3 Appendix B
Hepatitis B and C and HIV	X												
Urinalysis	X	as clinically indicated											Table 4 Appendix B

Appendix B Table 1 Schedule of assessments for AZD1775 + Carboplatin combination therapy

		AZD1775 and Carboplatin (cycle 21 days)									FOLLOW UP		For details see
	Screening	**Cycle 1**				**Cycle 2**		**Cycle 3 and beyond**			**End of study treatment visit (30 days FU) ± 2 days**	**Every 2 months (± 2 weeks)**	
Assesment	**Baseline (-28 to -1)**	**Day 1**	**Day 3**	**Day 8**	**Day 15**	**Day 1 (± 2 days)**	**Day 8 (± 2 days)**	**Day 1 (± 2 days)**	**Day 3**	**Day 8 (± 2 days)**			
Coagulation (PT/INR/PTT)	X	as clinically indicated											Table 2 appendix B
Pregnancy test	X	X				X		X					Section 6.2.1 of master protocol
Pharmacokinetics													
AZD1775 PK sample (plasma)			X[g]						X[g]				Section 6.4 of master protocol and Appendix B Table
CBDP PK sample (plasma)		X[h]						X[h]					Section 6.4 of master protocol and Appendix B Table
Monitoring													
WHO/ECOG performance status	X	X				X		X			X		Section 6.3.1 of master protocol

Appendix B Table 1 Schedule of assessments for AZD1775 + Carboplatin combination therapy

		AZD1775 and Carboplatin (cycle 21 days)									FOLLOW UP		For details see
	Screening	**Cycle 1**				**Cycle 2**		**Cycle 3 and beyond**			**End of study treatment visit (30 days FU) ± 2 days**	**Every 2 months (± 2 weeks)**	
Assesment	**Baseline (-28 to -1)**	**Day 1**	**Day 3**	**Day 8**	**Day 15**	**Day 1 (± 2 days)**	**Day 8 (± 2 days)**	**Day 1 (± 2 days)**	**Day 3**	**Day 8 (± 2 days)**			
AE/SAE assessment [i]	X	X	X	X	X	X	X	X	X	X	X	X[s]	Section 7 of master protocol
IP Administration													
CBDP[m, k]		X				X		X					Section 8.1.2 of Appendix B
Dispense AZD1775 Review/Collect Dosing Diary [j,l, n]		X				X		X					Section 8.1.1 of Appendix B
Study laboratory assessments													
mRNA		X											Section 6.6.1.4of master protocol
CCI [redacted]		X				X					X		Section 6.6.1.2 of

Appendix B Table 1 Schedule of assessments for AZD1775 + Carboplatin combination therapy

		AZD1775 and Carboplatin (cycle 21 days)									FOLLOW UP		For details see
	Screening	Cycle 1				Cycle 2		Cycle 3 and beyond			End of study treatment visit (30 days FU) ± 2 days	Every 2 months (± 2 weeks)	
Assesment	**Baseline (-28 to -1)**	**Day 1**	**Day 3**	**Day 8**	**Day 15**	**Day 1 (± 2 days)**	**Day 8 (± 2 days)**	**Day 1 (± 2 days)**	**Day 3**	**Day 8 (± 2 days)**			
													master protocol
Tumor biopsy (newly acquired or archival ≤3 years old)[ar]	X												Section 6.6.1.2 of master protocol
Tumor evaluation (CT or MRI) (RECIST 1.1)[o, p]	X	**q6w** ± 1week (relative to the date of first dose) until confirmed objective disease progression/death (whichever comes first).											Section 6.1 of master protocol
Subsequent anticancer therapy recording in eCRF												X	n/a
Survival status												X[s]	Section 6.1.1 of master protocol

[a] If laboratory or imaging procedures were performed for other reasons prior to signing consent, these can be used for screening purposes with consent of the patient. However, all screening laboratory and imaging results must have been obtained within 28 days of enrollment.

[b] Body weight is recorded along with vital signs.

[c] ECG is mandatory on Day 1 of each Cycle and could be done at other visits if clinically indicated. Any clinically significant abnormalities detected require triplicate ECG results.

[d] If screening laboratory assessments are performed within 3 days prior to Day 1 (first infusion day), they do not need to be repeated at Day 1. Serum or plasma chemistry, coagulation, hematology, and/or LFT monitoring may be performed more frequently if clinically indicated.

[e] Haematology results must be available prior to dosing of each cycle, and reviewed by the treating physician or Investigator according to the dose modification and safety management guidelines in Section 7.3

[f] For women of childbearing potential only. A urine or serum pregnancy test is acceptable. Women of childbearing potential are required to have a pregnancy test within 3 days prior to the first dose of study drug and then every 4 weeks. Pregnancy test may occur on Day 1, but results must be available and reviewed by the treating physician or Investigator prior to commencing an infusion

[g] Predose and C_{max} 2-4 hours post dose day 3 for alternate cycles starting from C1.

[h] Up to 60 minutes pre-dose and end of infusion, for alternate cycles starting from C. Pre-dose PK sample should be taken prior to the dosing of any study drug .

[i] For AEs/SAEs reported during screening, additional information such as medical history and concomitant medications may be needed.

[j] Five doses of AZD1775 (225 mg PO BID) will be taken in approximate 12-hour intervals over 2.5 days (Days 1-3). AZD1775 should be taken approximately 2 hours before or 2 hours after food.

[k] Results for serum or plasma chemistry and LFT monitoring must be available before commencing administration (within 3 days) and reviewed by the treating physician or Investigator prior to dosing.

[l] All patients must take a 5-HT3 antagonist prior to each dose of AZD1775, for example, ondansetron (ZOFRAN®) 8 mg PO BID or granisetron (KYTRIL®) 1 mg PO BID. The 5-HT3 antagonist may be given by IV if necessary.

[m] Carboplatin AUC 5 IV will be administered according to institutional standards on Day 1 of each 21-day cycle after AZD1775 dosing.

[n] Review AZD1775 dosing compliance with the patient at the beginning of each new treatment cycle when study drug is dispensed.

[o] RECIST 1.1 assessments will be performed on images from CT (preferred) or MRI, each preferably with IV contrast of the chest, abdomen (including liver and adrenal glands), and pelvis every 6 weeks (+/- 1 week). Pelvic imaging is recommended only when primary or metastatic disease in the pelvic region is likely. Additional anatomy should be imaged based on signs and symptoms of individual patients at baseline and follow-up. Baseline assessments should be performed no more than 28 days before the date of enrollment and, ideally, should be performed as close as possible to and prior to the start of the initial dose of IP.

[p] Patients will have scans done q6w for the first 48 weeks, and then q12w thereafter (relative to the date of first IP administration) until objective disease progression.

[r] If available patient's newly acquired or archival ≤3 years old tumor samples should be collected. Should there be no sample available no new biopsy is needed to be obtained.

[s] Following treatment discontinuation, assessments for survival and SAE/AE must be made monthly for the first 3 months and then every 2 months thereafter.

Note: All assessments on treatment days are to be performed prior to infusion, unless otherwise indicated.

AE Adverse event; C Cycle; CT Computed tomography; ECG Electrocardiogram; ECOG Eastern Cooperative Oncology Group; HIV Human immunodeficiency virus; IM Intramuscular; INR International normalized ratio; IP Investigational Product; LFT Liver function

test; MRI Magnetic resonance imaging; PD Progressive disease; PK Pharmacokinetic; PT Prothrombin time; PTT Partial thromboplastin time; q6w Every 6 weeks q8w Every 8 weeks; q12w Every 12 weeks; RECIST 1.1 Response Evaluation Criteria in Solid Tumors; SAE Serious adverse event; T_3 Triiodothyronine; T_4 Thyroxine; TSH Thyroidstimulating- hormone; WHO World health Organization.

5.1 Enrollment/screening period

All screening and enrollment procedures will be performed according to the assessment schedule in Appendix B Table 1. Demographic data and other characteristics will be recorded including date of birth or age, gender, smoking history, and race/ethnicity, according to local regulations. A standard medical and surgical history will be obtained.

Written informed consent and any locally required privacy act document authorization must be obtained prior to performing any protocol-specific procedures, including screening/baseline evaluations. If laboratory or imaging procedures were performed for other reasons prior to signing consent, these can be used for screening purposes with consent of the patient. However, all screening laboratory and imaging results must have been obtained within 28 days of enrollment. All patients will have the option to provide consent to supply a sample of their tumor (archived or newly acquired biopsy) for entry into this study. This consent is included in the main patient informed consent form.

Screening/baseline evaluations may be performed over more than 1 visit.

The timing of vital sign assessments should be such that it allows the blood draw (eg, PK blood sample) to occur at the time points indicated in Appendix B Table 1.

5.2 Treatment period

All procedures to be conducted during the treatment period will be performed according to the assessment schedule (see Appendix B Table 1).

Whenever vital signs and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: vital signs and then blood draws. The timing of the vital signs assessments should be such that it allows the blood draw (eg, PK blood sample) to occur at the time points indicated in Appendix B Table 1).

5.3 Follow-up period

All procedures to be conducted during the follow-up period will be performed according to the assessment schedule Appendix B Table 1).

6. STUDY ASSESSMENTS

Please also refer to Section 6 of the master protocol for the study assessments applicable to all arms in the study. Additional study assessments applicable to Arm B are listed below.

6.1 Safety Assessments

6.1.1 Laboratory safety assessments

The laboratory variables to be measured are presented in Table 2 (clinical chemistry), Table 3 (hematology), and Table 4 (urinalysis).

Other safety tests to be performed at screening include assessment for hepatitis B surface antigen, hepatitis C antibodies, and human immunodeficiency virus antibodies.

The following laboratory variables will be measured:

Appendix B Table 2 Laboratory - clinical chemistry

Albumin	Lipase[b]
Alkaline phosphatase[a]	Magnesium[c]
ALT[a]	Potassium
Amylase[b]	Sodium
AST[a]	Total bilirubin[a]
Bicarbonate[c]	Total protein
Calcium	TSH
Chloride[c]	T3 free[d] (reflex)
Creatinine clearance[c]	T4 free[d] (reflex)
Creatinine	Urea or blood urea nitrogen, depending on local practice
Gamma glutamyltransferase[c]	
Glucose	
Lactate dehydrogenase	

[a] Tests for ALT, AST, alkaline phosphatase, and total bilirubin must be conducted and assessed concurrently. If total bilirubin is >2 × upper limit of normal (and evidence of Gilbert's syndrome), then fractionate it into direct and indirect bilirubin.

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

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

[d] Free T3 and T4 will only be measured in Arm A if TSH is abnormal or if there is a clinical suspicion of an AE related to the endocrine system.

AE Adverse event; ALT Alanine aminotransferase; AST Aspartate aminotransferase; T3 Triiodothyronine; T4 Thyroxine; TSH Thyroid-stimulating hormone.

Appendix B Table 3 Laboratory – hematology

Basophils	Monocytes
Eosinophils	Neutrophils
Hematocrit	Platelet count
Hemoglobin	Red blood cell count
Lymphocytes	Total while blood cell count
Mean corpuscular hemoglobin	Activated partial thromboplastin time
Mean corpuscular hemoglobin concentration	International Normalized Ratio
Mean corpuscular volume	Partial thromboplastin time

Note: For coagulation parameters, activated partial thromboplastin time, partial thromboplastin time and international normalized ratio are to be assessed at baseline and as clinically indicated.

Note: absolute values of blood cells should be provided where possible rather than percentages (e.g. for white cell differential counts)

Appendix B Table 4 Laboratory – urinalysis

Bilirubin	Ketones
Blood	pH
Color and appearance	Protein
Glucose	Specific gravity

Note: Urinalysis must be done at baseline and then as clinically indicated.

Note: Microscopy should be used as appropriate to investigate white blood cells and use the high power field for red blood cells.

6.1.2 ECG

A 12-lead safety ECG (paper ECG printout of 10 seconds for Investigator review) will be taken at screening and prior to dosing on day 1 of each study cycle.

Triplicate ECG recordings should be taken within an approximate 5-minute period. Additional ECGs may be taken at any other time the Investigator deems necessary for safety during the administration period. The patients will rest for at least 10 minutes before the start of each recording and they must be in the same supine body position (maximum 30 degrees flexion in the hip and feet not in contact with the footboard) at the recording time point.

The Investigator will judge the overall interpretation as normal or abnormal. If abnormal, it will be decided as to whether or not the abnormality is clinically significant or not clinically significant. The paper copy of each ECG reading will be retained with the patient's completed source documents. Only overall evaluation (normal/abnormal) will be recorded in the eCRF. If there is a clinically significant abnormal unscheduled ECG finding during the treatment

period, this should be recorded on the AE eCRF, according to standard AE collection and reporting processes (see Section 7).

Attention should be paid to any detected increases in QTc interval. Patients who develop a single resting value of QTc interval of >450 msec/male and >470 msec/female or a shift from baseline of ≥60ms should stop taking AZD1775. Dosing can be resumed at a reduced dose after return of the resting QTc interval to pre-treatment status has been confirmed and correction of possible electrolyte imbalance has been made (see Appendix B Table).

Monitoring of QTc, checking and correction of abnormal electrolyte levels and renal function are advised, especially in case of severe/prolonged diarrhoea. If QTc increases markedly from baseline, but stays below the above limits, a cardiologist's advice should be sought.

The concomitant use of ondansetron (known to prolong the QTc interval in rare cases, per labelling) should be taken into account when interpreting QTc changes.

6.2 Pharmacokinetics

6.2.1 Collection of blood pharmacokinetic samples

Sparse PK samples will be collected for AZD1775 and CBDP during the study on Cycle 1 and at alternate cycles at the time points specified in Appendix B Table . The date and actual time of the PK sample will be recorded.

Appendix B Table 5 PKs: Carboplatin and AZD1775

	Cycle 1, Cycle 3 and beyond[a]			
	Day 1		**Day 3 [a b]**	
Timing	Predose	End of infusion	Pre-dose	2-4 hr
PK sample for Carboplatin	X	X		
PK samples for AZD1775			X	X

[a] Alternate cycles (e.g Cycles, 3,5,7 etc.)
[b] ±15 minutes.
PK Pharmacokinetics

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

6.3 Efficacy Analysis

See Section 6.1 of the master protocol.

Efficacy in Arm B will be assessed using RECIST 1.1 criteria on images collected at baseline and then every 6 weeks ± 1 week until objective disease progression or off-study.

It is important to follow the assessment schedule as closely as possible (see Appendix B Table 1). If an unscheduled imaging assessment is performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at his or her next regularly scheduled imaging visit.

6.4 Biomarker analysis

Additional tumor based biomarkers that may be analyzed to investigate DNA damage/repair mechanisms related to AZD1775 include but are not limited to CCI [redacted]

Whole blood samples will be collected for CTC analysis at predose on Cycle 1 Day 1, Cycle 2 Day 1 and End of Treatment. Details for processing, handling, and shipping are provided in the Laboratory Manual.

In addition, select samples taken for collection of CCI [redacted] may be processed to generate circulating tumor DNA or blood samples may be collected in Streck DNA BCT tubes, and processed to isolate CCI [redacted]. Additional samples may be taken to generate circulating mRNA for storage and subsequent analyses. CCI [redacted]

7. SAFETY REPORTING AND MEDICAL MANAGEMENT

Please refer to Section 7 of the master protocol for details of reporting AEs, SAEs, AEs of special interest, paternal exposure, and management of investigational product (IP) related toxicities applicable to all arms in the study. Additional details for reporting AE, SAEs, AEs of special interest, paternal exposure, and management of IP-related toxicities applicable to Arm B are described below.

7.1 Reporting of adverse events

7.1.1 Time period for collection of adverse events

AEs and SAEs will be recorded from the time of informed consent, throughout the treatment period, and including the follow-up period (the follow-up period is 30 days after the last dose of study treatment of AZD1775 or CBDP). SAEs occurring in the follow-up period should be reported in the usual manner.

7.1.2 Follow-up of unresolved adverse events

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

7.1.3 Reporting of serious adverse events

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

If any SAE occurs in the course of the study, Investigators or other site personnel must inform appropriate AstraZeneca representatives immediately or no later than 24 hours of when he or she becomes aware of it.

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

In addition to standard SAE reporting process, the SCRI Innovations Safety Department will be notified about new SAE by sending automatic e-mail alert to SCRI Innovations SAE mailbox: CANN.SAE@SCRIInnovations.com.

Automatic e-mail alert about follow-up information for SAEs and information on non-serious AEs that become serious should also be sent to SCRI Innovations Safety Department as soon as it is available.

The detailed SAE reporting process will be provided to the sites in the SAE reporting guidelines contained in the trial reference manual.

Investigators must report SAEs and follow-up information to their responsible Institutional Review Board (IRB) according to the policies of the responsible IRB. For fatal or life threatening AEs where important or relevant information is missing, active follow up is undertaken immediately.

AstraZeneca or their representative will provide Regulatory Authorities, Ethics Committees, and Principal Investigators with clinical safety updates/reports according to local requirements.

7.1.4 Post study events

After the patient has been permanently withdrawn from the study, there is no obligation for the Investigator to actively report information on new AEs or SAEs occurring in former study patients after the armdesignated- number of days, or 30-day safety follow-up period. However, if an Investigator learns of any SAEs, including death, at any time after the patient has been permanently withdrawn from the study, and he/she considers there is a reasonable possibility that the event is related to the study treatment, the Investigator should notify AstraZeneca, Patient Safety, or its representative.

7.2 Pregnancy

7.2.1 Maternal exposure

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

If any pregnancy occurs in the course of the study, the Investigator or other study center personnel must inform the appropriate AstraZeneca representatives within 1 calendar day (ie, immediately but no later than 24 hours of when he or she becomes aware of it).

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs, and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

7.2.2 Paternal exposure

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

7.3 Dose modifications and management of investigational product-related toxicities

Guidelines for the management of hematological and non-hematological AEs for AZD1775 and CBDP are described below.

Toxicity will be assessed utilizing the NCI Common Terminology Criteria for Adverse Event (CTCAE) version 4.03 unless otherwise specified.

Dose adjustments will be based on the organ system exhibiting the greatest degree of toxicity. Dose reductions or holds and initiation of supportive care are allowed as clinically indicated by the treating physician. Any patient requiring a toxicityrelated- dose delay of more than 28 days from the intended day of the next scheduled dose must be discontinued from the study unless there is approval from the Study Physician for the patient to continue. If Day 1 treatment with either AZD1775 or CBDP is interrupted, then both study medications will be

delayed until the combination can be resumed. See Appendix B Table and Appendix B Table for dose level reductions.

Appendix B Table 6 AZD1775 dose level reductions for toxicity

AZD1775 Starting Dose[a]	AZD1775 -1 level	AZD1775 -2 level
225 mg BID (5 doses over 2.5 days)	175 mg BID (5 doses over 2.5 days)	125 mg BID (5 doses over 2.5 days)

[a] AZD1775 twice daily taken in 12 hour intervals over 2.5 days on Days 1-3

BID twice daily

Appendix B Table 7 CBDP dose level reductions for toxicity

CBDP Starting Dose[a]	CBDP -1 level	CBDP -2 level
AUC 5	AUC 4	AUC 3

[a] CBDP is administered on Day 1 of each 21-day cycle.

AUC Area under the plasma drug concentration-time curve; CBDP carboplatin

7.3.1 Dose modifications due to hematologic-related adverse events

Hematologic panel (complete blood counts, 5-part differential [neutrophils, lymphocytes, monocytes, basophils and eosinophils], and platelets) will be obtained for all patients **at the beginning of each treatment cycle (Day 1) and reviewed prior to dose administration**. If hematologic toxicity occurs (Appendix B Table 8), treatment should be held and ANC and platelets should be monitored at least weekly until recovery. Patients should be managed as medically indicated. Treatment should not be resumed **until recovery to Grade 1** (ANC ≥1.5 x 10^9/L or 1,500/ µL; platelets ≥75,000/ µL).

Appendix B Table 8 Hematologic dose modifications and management

Neutrophil and Platelet Blood Counts and Study Drug Action								
Neutrophil count	**Action AZD1775**	**Action chemo**	**2nd event**	**Action AZD1775**	**Action chemo**	**3rd event**	**Action AZD1775**	**Action chemo**
Grade 2 <1.5-1.0 x10^9/L	Hold Resume at same dose	Hold Resume at same dose		Hold Resume at DL-1	Hold Resume at same dose		Hold Resume at DL-2	Hold Resume at DL-1
Grade 3 <1.0-0.5 x10^9/L	Hold Resume at DL-1	Hold Resume at same dose		Hold Resume at DL-2	Hold Resume at DL-1		Hold Resume at DL-2	Hold Resume at DL-2

Neutrophil and Platelet Blood Counts and Study Drug Action

Grade 3 <1.0-0.5 x10^9/L with documented infection and/or fever	Hold Resume at DL-1	Hold Resume at DL-1		Hold Resume at DL-2	Hold Resume at DL-2		Hold Contact Medical Monitor	Hold Contact Medical Monitor
Grade 4 <0.5 x10^9/L	Hold Resume at DL-1	Hold Resume at DL-1		Hold Resume at DL-2	Hold Resume at DL-2		Discontinue and follow for disease progression	Discontinue and follow for disease progression
Grade 4 Febrile neutropenia or Grade 4 Infection with neutropenia	Discontinue and follow for disease progression	Discontinue and follow for disease progression						
Platelet count	**Action AZD1775**	**Action chemo**	**2nd event**	**Action AZD1775**	**Action chemo**	**3rd event**	**Action AZD1775**	**Action chemo**
Grade 2 75,000-50,000/ µL	Hold Resume at same dose	Hold Resume at same dose		Hold Resume at DL-1	Hold Resume at same dose		Hold Resume at DL-1	Hold Resume at DL-1
Grade 3 50,000-25,000/ µL	Hold Resume at DL-1	Hold Resume at same dose		Hold Resume at DL-2	Hold Resume at DL-1		Hold Resume at DL-2	Hold Resume at DL-2
Grade 4 <25,000/ µL without any evidence of bleeding	Hold Resume at DL-1	Hold Resume at DL-1		Hold Resume at DL-2	Hold Resume at DL-2		Discontinue and follow for disease progression	Discontinue and follow for disease progression
Thrombocytopenic haemorrhage (gross occult bleeding) associated with platelet count <50,000/ µL	Discontinue	Discontinue						

Neutrophil and Platelet Blood Counts and Study Drug Action

[a] If hematologic toxicity parameters do not recover within 28 days, the patient should be removed from the study treatment.
ANC Absolute neutrophil count

Please consider using G-CSF in the event of severe neutropenia or febrile neutropenia according to institutional standards.

No more than two dose reductions will be allowed for any patient. Patients requiring further dose reduction due to toxicity must discontinue study treatment. Dose re-escalation is not allowed. If the patient has concurrent neutropenia and thrombocytopenia, please follow the most conservative guidance in the table below and discuss with Medical Monitor AstraZeneca Study Physician as needed.

7.3.2 Dose modifications due to non-hematologic related adverse events

Dose modifications for non-hematologic toxicities should be based on toxicities occurring during the previous cycle. For toxicities that lead to a dose reduction, the dose will not be re-escalated during subsequent cycles.

Any patient who develops a Grade 3 or 4 non-hematologic toxicity that does not resolve to ≤ Grade 1 within 28 days should be discontinued from the study treatment. However, if the Investigator determines that the non-hematologic toxicity was due to one study drug and not the other, treatment with the remaining study drug may continue as clinically appropriate.

Based upon the maximum non-hematologic toxicities experienced during the previous cycle, dose adjustments for subsequent cycles are to be made according to the criteria defined in Appendix B Table 9 (unless specified per unique toxicities as noted below).

Appendix B Table 9 Non-hematologic toxicity dose modification and management

Electrocardiogram QT corrected interval prolonged		
QTc Value	CBDP	AZD1775
QTc 450-480 ms (males) or 470-480 (females)	No dose modifications	Hold. Once QTc interval has returned to pretreatment status and correction of possible electrolyte imbalance has been made, resume at next lower dose level.
QTc 481-500 ms	No dose modifications	Hold. Seek cardiologist advice.

QTc ≥ 501 ms	Discontinue treatment	Discontinue treatment
Shift from baseline of ≥ 60ms	Discontinue treatment	Discontinue treatment

CTCAE version 4.03	**CBDP**	**AZD1775**
Grade 0 - 2	No dose modification	No dose modification
Grade 3[b,c,d]	Hold[a]	Hold[a]
Grade 4[b]	Hold until toxicity resolves to Grade ≤1. Resume with 1 dose level reduction	Hold until toxicity resolves to Grade ≤1. Resume with 1 dose level reduction
Second repeat incidence of Grade 3 or 4 toxicity (except nausea, vomiting, fatigue, malaise, lethargy, anorexia, alopecia)	Discontinue treatment	Discontinue treatment

Hepatic

CTCAE v4.03	**CBDP**	**AZD1775**
Grade 1-2	No dose modification	No dose modification
Grade 3 or 4 (manifested as elevations in ALT, AST, ALP, or bilirubin)	Hold until resolves to Grade ≤1 or baseline, then resume CBDP with a 1 level dose reduction. If not resolved within 28 days, discontinue CBDP.	Hold until resolves to Grade ≤1 or baseline, then resume study drug with a 1 level dose reduction. If not resolved within 28 days, discontinue study drug.

Diarrhea or mucositis

CTCAE v4.03	**CBDP**	**AZD1775**
Grade 1-2	No dose modification	No dose modification
Grade 3 or 4 (or requiring hospitalization)	Hold[a]	Hold[a]

Nephrotoxcity

CTCAE v4.03	**CBDP**	**AZD1775**
Grade 0-1	No dose modification	No dose modification

Grade ≥ 2	Hold until resolves to Grade ≤1 or baseline, then resume CBDP with a 1 level dose reduction. If not resolved within 28 days, discontinue CBDP.	Hold[a]

Neurotoxicity		
CTCAE v4.03	**CBDP**	**AZD1775**
Grade 1	No dose modification	No dose modification
Grade 2	Hold until toxicity resolves to Grade ≤1. Resume with 1 dose level reduction.	No dose modification
Grade 3 or 4	Discontinue treatment	Discontinue treatment

[a] Hold until toxicity resolves to ≤Grade 1 and then resume at the same dose with no modification.
[b] Dose reduction for nausea and vomiting should be made only if Grade 3 or Grade 4 toxicity occurs in spite of maximum anti-emetics.
[c] For a Grade 3 pulmonary embolism, the dose should be held but the subsequent doses do not have to be reduced 1 dose level, at the Investigator's discretion.
[d] Grade 3 electrolyte value(s) (ie, hypokalaemia) do not require a dose reduction once the electrolyte is ≤Grade 1.

7.3.3 Non-hematologic toxicity management guidelines

7.3.3.1 Gastrointestinal system disorders

Gastrointestinal AEs including nausea, vomiting, and diarrhea have previously been associated with AZD1775 treatment. These types of toxicities observed in AZD1775 studies are not unexpected for therapies that include full-dose chemotherapy. Patients should therefore be closely monitored for signs of gastrointestinal AEs and, if necessary, they should be managed clinically with supportive treatment not limited to anti-emetics, IV hydration, and anti-diarrheal treatment as needed. Weight should be carefully monitored with other vital signs and doses of AZD1775 adjusted accordingly.

Following the receipt of 3 SAEs of gastrointestinal haemorrhagic events from ongoing studies, this topic has been identified as a new important potential risk to be kept under close surveillance with immediate attention given to any case report received events.

7.3.3.2 Diarrhea

Due to frequent reports of diarrhea with AZD1775 administration, vigorous anti-diarrheal treatment loperamide (Imodium®) is required at the first onset of diarrhea, according to the American Society of Clinical Oncology guidelines. Oral loperamide 4 mg should be administered every 2 hours until diarrhea-free for at least 12 hours. The first dose of

loperamide could be lowered to 2mg if the diarrhoea is recurrent and if, in the opinion of the treating physician, the diarrhoea is not severe.

Patients should be instructed to notify the Investigator or research staff of the occurrence of bloody or black stools, symptoms of dehydration, fever, inability to take liquids by mouth, and inability to control diarrhea within 24 hours of using loperamide or other prescribed anti-diarrhoeal medications.

If diarrhea is severe (ie, requiring IV rehydration) and/or associated with fever or severe neutropenia (Grade 3 or 4), broad-spectrum antibiotics must be prescribed. Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting should be hospitalised for IV hydration and correction of electrolyte imbalances.

7.3.3.3 Nausea and vomiting

All patients must receive a 5-HT3 antagonist, ondansetron (ZOFRAN®) 8 mg PO BID or granisetron (KYTRIL®) 1 mg PO BID prior to each dose of AZD1775. Additional doses of 5-HT3 antagonist may be used if needed. In addition, dexamethasone 4 mg PO will be given with each AZD1775 dose, unless contraindicated or not well-tolerated. Dexamethasone may be continued on further days of dosing, potentially at a lower dose. Dexamethasone or the 5-HT3 antagonist may be given by IV. Promethazine (PHENERGAN®), prochlorperazine (COMPAZINE®), and benzodiazepine may still be used as additional adjunctive treatments during AZD1775 therapy. **Please note: aprepitant [Emend] and fosaprepitant are not permitted due to known DDIs.**

Patients should be strongly encouraged to maintain liberal oral fluid intake.

Suitable alternative medications may be used, with adequate justification, in those studies where the use of any of the above medications might interfere with other study procedures or are deemed insufficient.

7.3.3.4 Motor neuropathy or muscle weakness

Any onset of Grade >2 motor neuropathy or Grade >2 muscle weakness should be evaluated by an electromyogram to rule out the possibility of chronic inflammatory demyelinating polyneuropathy (CIDP). With a diagnosis of CIDP, the patient should be discontinued from study treatment.

7.3.3.5 Dose modifications for infusion reactions

Infusion reactions (eg, rash, urticaria, erythema, pruritus, bronchospasm, and hypotension) can occur with the agents used in this study. There is increased risk of a reaction with CBDP. CBDP must be discontinued in patients experiencing a Grade 3 or 4 infusion reaction during treatment.

To identify the grade of a reaction, refer to the list below adapted from the General Disorders and Administration Site Conditions section of the NCI CTCAE version 4.03:

Grade 1: Mild transient reaction; infusion interruption not indicated; intervention not indicated

Grade 2: Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, IV fluids indicated for ≤24 hours)

Grade 3: Prolonged (eg, not rapidly responsive to symptomatic mediation and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae. Any infusion that is interrupted and not resumed within the visit will be considered a Grade 3 reaction.

Grade 4: Life-threatening consequences; urgent intervention indicated

7.3.3.6 QTc prolongation

The QTc interval will be measured in 12-lead ECGs at baseline and at the commencement of each treatment cycle; and an assessment made of the emergence, if any, of QTc prolongation. Serum electrolyte levels should be obtained at baseline and at commencement of each treatment cycle.

Checking and correction of abnormal electrolyte levels and renal function are advised, especially in case of diarrhoea.

The administration of AZD1775 with substances known to prolong the ECG QTc interval is not recommended.

Special note: The potential risk of concomitant use of AZD1775 with ondansetron (known to prolong the QTc interval) should be taken into account.

Dose modifications or discontinuations for patients experiencing QTc prolongations are summarized in Appendix B Table above.

8. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

8.1 Identity of investigational product(s)

Investigational product	Dosage form and strength
AZD1775	25 mg or 100 mg capsules
CBDP [a]	IV sourced locally

[a] Under certain circumstances when local sourcing is not feasible, standard of care treatment may be supplied centrally through AstraZeneca

8.1.1 AZD1775

AstraZeneca will supply AZD1775 capsules for oral use. The capsules will be supplied at 2 strengths (100 and 25 mg) in high-density polyethylene bottles, which sufficiently protects the drug from light. The different capsule strengths should not be combined in the same bottle at any time. Additional information about the IP may be found in the IB.

AZD1775 225 mg is taken PO in approximately 12-hour intervals BID over 2.5 days on Days 1 to 3 of each treatment cycle. Treatment cycles are every 21 days. AZD1775 should be taken with 8 ounces of water approximately 2 hours before or 2 hours after food. All patients must take a 5-HT3 antagonist prior to each dose of AZD1775, for example, ondansetron 8 mg PO BID or granisetron 1 mg PO BID. The 5-HT3 antagonist may be given by IV if necessary.

If a patient misses 1 of the 2 daily doses according to schedule, the dose should be taken as soon as possible, but not more than 6 hours after the missed dose was scheduled. If greater than 6 hours, the missed dose should be skipped, and the patient should take the next dose when scheduled.

If vomiting occurs after a patient takes the AZD1775 dose, the patient should be instructed not to retake the dose but to wait until the next scheduled dose of AZD1775. If no dose is scheduled for the following day, the dose will not be 'made up'. If vomiting persists, the patient should contact the Investigator.

8.1.2 Carboplatin

Area under the Curve (AUC) 5 IV Day 1 every 21 days

CBDP, at a dose calculated to produce an AUC of 5, will be administered by IV infusion according to institutional standards.

The CBDP dose will be calculated using the Calvert formula based on the patient's GFR, which is estimated by using the CrCl.

Calvert formula: CBDP dose (mg) = target AUC × (GFR + 25)

The Food and Drug Administration (FDA) has recommended that physicians consider capping the dose of CBDP for the desired exposure (AUC) to avoid potential toxicity due to overdosing for all laboratories using the isotope dilution mass spectrometry derived serum creatinine measurements. Therefore, the maximum dose of CBDP should be based on a CrCl no greater than 125 mL/min for patients with normal renal function. In these, CBDP can be safely dosed according to the instructions in the drug's labelling. Refer to the US FDA, Center for Drug Evaluation and Research website (http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm228974.htm) for more specific guidelines.

Cockcroft-Gault formula:

$$\text{CrCl (GFR)} = \frac{[(140 - \text{age}) \times (\text{wt. in kg})] \times (0.85 \text{ if female})}{(72 \times \text{serum creatinine [mg/dL]})}$$

Patients may receive prophylactic anti-emetic therapy for moderately emetogenic chemotherapy according to institutional standards, excluding aprepitant Emend.

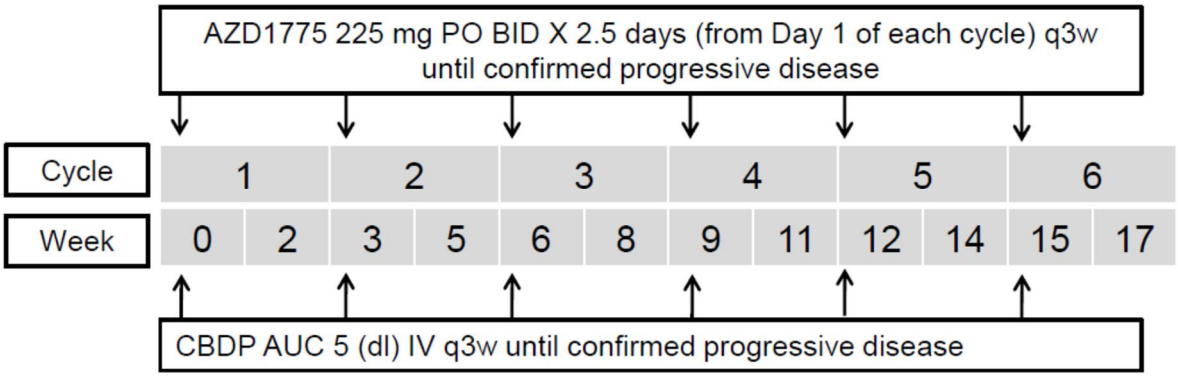
Refer to the CBDP package insert for additional information.

8.2 Dose and treatment regimens

For Arm B, up to 20 eligible patients will be enrolled, and all patients will receive:

AZD1775 225 mg BID PO for 2.5 days from Day 1 + CBDP AUC 5 Day 1 IV; q3w until PD

Appendix B Figure 2 AZD1775 + carboplatin therapy dosing schedule



AZD1775 should be administered first, then followed by carboplatin infusion.

8.3 Labeling

Please refer to Section 8.3 of the master protocol for details regarding labelling applicable to all arms.

8.4 Storage

Please see Section 8.4 of the master protocol.

8.5 Compliance

AZD1775 dosing compliance will be reviewed with the patient at the beginning of each new treatment cycle when AZD1775 is dispensed. All patients will be required to complete a dosing diary, which must be returned to the clinic for review at each visit. The patient should be instructed to record each date and time the dose(s) was taken in the dosing diary. If a dose

is missed, the reason must be noted in the diary. A copy of the dosing diary is provided in the study reference materials.

Patients should be advised to return any unused AZD1775 in the original bottles, in addition to returning any empty bottles.

The administration of all study drugs (including IPs) should be recorded in the appropriate sections of the case report form (CRF).

8.6 Accountability

Please see Section 8.6 of the master protocol.

8.7 Concomitant and other treatments

Please refer to Section 8.7 of the master protocol for details regarding concomitant and other treatments applicable to all arms. Details regarding concomitant and other treatments applicable to Arm B are described below.

8.7.1 Prohibited concomitant medications

- No formal clinical drug interaction studies have been performed with AZD1775. An exploratory assessment of the effect of aprepitant on AZD1775 exposure in oncology patients suggests that there is a drug interaction between AZD1775 and aprepitant, as exposure to AZD1775 increased by ~60% when aprepitant was coadministered with AZD1775. The observed increase in AZD1775 exposure is likely the result of CYP3A4 inhibition by aprepitant. This increase in exposure is statistically significant. At the selected MTD, this increase may also be of clinical importance. Therefore, concomitant treatment with aprepitant and fosaprepitant is not allowable per protocol until further evaluation.

- Potent or moderate inhibitors or inducers of CYP3A4, sensitive CYP3A4 substrates, and CYP3A4 substrates with a narrow therapeutic window should be avoided until additional data on drug-drug interaction becomes available. The use of sensitive substrates of CYP3A4, such as atorvastatin, simvastatin and lovastatin, is prohibited in this study. As grapefruit and Seville oranges are known to contain moderate inhibitors of CYP3A4, these fruits or their products (including marmalade, juice, etc.) should be avoided while taking AZD1775.

- *In vitro* data suggests that AZD1775 may also be a weak reversible inhibitor of CYP2C19. Caution should be exercised with concomitant administration of AZD1775 and agents that are sensitive substrates of CYP2C19, or substrates of this enzyme with narrow therapeutic range; refer to Appendix I for a list of sensitive substrates of CYP2C19, or substrates of this enzyme with narrow therapeutic range.

- AZD1775 has been shown to be a weak inducer of CYP1A2 *in vitro* with a maximum measured response between donors of 39.9% to 93.1% (at 10 μM) and 18.6% to 32.5% (at 5 μM) of the positive control omeprazole (50 μM), respectively. Given the nature of the AZD1775 dosing schedule, however, the risk of induction in the clinic is considered low. No specific precautions are recommended at this time, except to be initially vigilant when using substrates of CYP1A2 with a narrow therapeutic range.

- *In vitro* studies have shown that AZD1775 may be a substrate and inhibitor for human P glycoprotein (P-gp). Caution should be exercised when agents that are inhibitors or substrates of P-gp are administered concomitantly with AZD1775 (see Appendix I).

- Recent *in vitro* transporter studies have shown AZD1775 to be an inhibitor of breast cancer resistance protein (BCRP) [median inhibition concentration 5.1 μM]. This finding is particularly relevant for drugs administered PO where exposure is normally limited by BCRP-mediated efflux, in particular some statins. Modeling has predicted a substantial increase in the exposure of atorvastatin when co-administered with AZD1775, and the use of atorvastatin is therefore prohibited in the current study. Other drugs where the disposition is mediated via BCRP should be administered with caution, dose modification considered, or substituted by an alternative drug.

- Metformin should be used with caution. AZD1775 has been shown to be an inhibitor of multi-antimicrobial extrusion protein (MATE) 1 and MATE2K transporters. A drug interaction with substrates of either transporter cannot be ruled out, the most important substrate known to date being metformin.

- Herbal preparations/medications are not allowed throughout the study. These herbal medications include, but are not limited to: St. John's wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone, yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 7 days prior to first dose of AZD1775.

- Avoid concomitant use of strong CYP3A inhibitors and moderate CYP3A inhibitors: azole antifungals (ketoconazole itraconazole, fluconazole, and voriconazole), macrolide antibiotics (erythromycin and clarithromycin), cimetidine, HIV protease inhibitors, and nefazodone

- Avoid concomitant use of strong CYP3A inducers and moderate CYP3A inducers: phenytoin, barbiturates, and rifampicin

8.7.2 Prohibited concomitant medications: CBDP

CBDP has limited nephrotoxic potential, but concomitant treatment with aminoglycosides has resulted in increased renal and/or audiologic toxicity, and caution must be exercised when a patient receives both drugs. Although peripheral neurotoxicity is infrequent, its incidence is increased in patients older than 65 years and in patients previously treated with cisplatin. Pre-

existing cisplatin-induced neurotoxicity does not worsen in about 70% of the patients receiving CBDP as secondary treatment.

8.7.3 Substances known to prolong the ECG QTc interval

The administration of AZD1775 with substances known to prolong the ECG QTc interval is not recommended. (See Appendix I Disallowed Medications and Medications to be Administered with Caution).

Special note: The potential risk of concomitant use of AZD1775 with ondansetron (known to prolong the QTc interval) should be taken into account.

8.7.4 Other concomitant treatment

Other medication other than that described above, which is considered necessary for the patient's safety and well-being, may be given at the discretion of the Investigator and recorded in the appropriate sections of the CRF.

9. STATISTICAL ANALYSES BY ASTRAZENECA

Please refer to Section 9 of the master protocol for details regarding statistical analyses applicable to all arms. Additional details regarding statistical analyses applicable to Arm B are described below.

9.1Adverse events

AEs observed up to 30 days following discontinuation of study treatment or until the initiation of the first subsequent therapy following discontinuation of treatment (whichever occurs first) will be used for the reporting of AE summary tables. This will more accurately depict AEs attributable to study treatment only, as a number of AEs up to 30 days following discontinuation of the study treatment are likely to be attributable to subsequent therapy.

9.2 Study and data management by Astrazeneca

Please refer to Section 10 of the master protocol for details of study and data management.

10. ETHICAL AND REGULATORY REQUIREMENTS

Please refer to Section 11 of the master protocol for details of ethical and regulatory requirements.

APPENDIX B1 NEW YORK HEART ASSOCIATION CRITERIA

Stages of Heart Failure – New York Heart Association Classification

Class I (Mild)
No Limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).

Class II (Mild)
Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.

Class III (Moderate)
Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity results in fatigue, palpitation, or dyspnea.

Class IV (Severe)
Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, physical discomfort is increased.

Reference
The Criteria Committee of the New York Heart Association. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston (MA): Little Brown & Co;1994:253-256.

APPENDIX C ARM C: CERALASERTIB (AZD6738) + OLAPARIB SUB-PROTOCOL

1. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC	Area under the plasma drug concentration-time curve
AUC(0-∞)	Area under the plasma drug concentration-time curve time 0 to infinity
BCRP	Breast cancer resistance protein
BID	Twice daily
CBDP	Carboplatin
CIDP	Chronic inflammatory demyelinating polyneuropathy
$C_{max,ss}$	Maximum plasma concentration at steady state
CrCl	Creatinine clearance
CRF	Case report form (electronic/paper)
CTCAE	Common Terminology Criteria for Adverse Event
CYP	Cytochrome P
DHEA	Dehydroepiandrosterone
DNA	Deoxyribonucleic acid
DLT	Dose-limiting toxicity
DTIC	Dacarbazine chemotherapy
ECG	Electrocardiogram
eCRF	Electronic case report form
ECOG	Eastern Cooperative Oncology Group

Abbreviation or special term	Explanation
ED-SCLC	Extensive-stage small-cell lung cancer
5-FU	5-fluorouracil
FDA	Food and Drug Administration
GFR	Glomerular filtration rate
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
IRB	Institutional Review Board
IP	Investigational product
IR	Ionising radiation
IV	Intravenous
MATE	Multi-antimicrobial extrusion protein
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
p53	Tumor protein 53 (protein product of TP53 gene)
P-gp	P glycoprotein
PD	Progressive disease
PFS	Progression-free survival
PO	By mouth
PK	Pharmacokinetic(s)
PR	Partial response
q3w	Every 3 weeks
q4w	Every 4 weeks
q6w	Every 6 weeks
q12w	Every 12 weeks

Abbreviation or special term	Explanation
RECIST 1.1	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SD	Stable disease
SCLC	small cell lung cancer
TP53	Gene encoding tumour protein 53
ULN	Upper limit of normal
WoCBP	Women of childbearing potential

2. INTRODUCTION

2.1 Background and rationale for conducting this study

Study D419QC00002 is an open-label, multicenter, multiarm, Phase II study in patients with extensive-stage small cell lung cancer (ED SCLC) who have refractory or resistant disease, defined as patients who progress during first-line platinum based chemotherapy or those who progress within 90 days after completing first-line platinum based chemotherapy. Study D419QC00002 is modular in design, allowing evaluation of the safety, tolerability, pharmacokinetics (PK) and anti tumor activity of different combinations of novel anti cancer agents in patients with refractory or resistant ED-SCLC, and will consist of a number of study arms, each evaluating the safety and tolerability of a specific combination.

Arm C in Study D419QC00002 investigates the efficacy, safety, and tolerability of ceralasertib (PO), an inhibitor of the ataxia telangiectasia and RAD3-related kinase (ATR), in combination with olaparib (PO), trade name Lynparza, in ED SCLC patients.

Small cell lung cancers (SCLCs) harbor multiple genomic alterations involved in cell cycle regulation, oncogenic signaling, and double-strand break repair. The most common genetic alterations in SCLC occur in: TP53 (90%), retinoblastoma 1 (RBI, 85%) (Byers et al 2012), MYC (cMYC, MYCN, and MYCL1, ~5% each), RAS (2%), and BRCA1/2 (3%). These alterations, and in particular, combinations of these alterations, force cancer cells to depend on the G2-M checkpoint for restoring cell cycle function and division. It is estimated that 18% of SCLCs harbor mutations in cell cycle regulation (TP53) and in oncogenic signalling (MYC or RAS). Likewise, 3% of SCLCs harbor mutations in both cell cycle regulation (TP53) and DSB repair (BRCA1/2).

ATR is an apical kinase in one of the DNA-damage induced checkpoint pathways that is crucial for the cell's response to replication stress (RS) (reviewed in Marechal and Zou 2013). RS occurs when replication forks stall due to unrepaired DNA strand breaks or the presence of covalent adducts formed by reactive metabolites or xenobiotics, including chemotherapies, generating segments of single-stranded DNA that is coated by replication protein A (RPA). RPA recruits ATR to sites of replication stress, furthing stalling fork progression and firing of new replication origins, and allowing the damaged DNA to be repaired. Any treatment that causes RS, increases dependence on ATR, and inhibition of ATR under such circumstances is expected to lead to mitotic catastrophe and cell death. Synergy with ATR inhibition is expected with various treatments, including ionizing radiation, overtly DNA damaging chemotherapy and other targeted agents, especially those that impact DNA damage repair. ceralasertib is a potent inhibitor of ATR kinase with a significant margin over structurally related kinases.

Olaparib is an inhibitor of poly-ADP ribose polymerase, an enzyme that is crucial for the repair of single strand DNA breaks as part of base excision repair (BER) (reviewed in O'Connor 2015). Inhibition of the PARP enzymes leads to the accumulation of single-strand DNA breaks, which if not repaired are converted to double strand DNA breaks during DNA

replication. The accumulation of double strand DNA breaks by treatment with olaparib activates the cell's repair machinery and tumours that are defective in the detection and repair of double strand DNA breaks, such as those with BRCA1 or BRCA2 gene mutations, are exquisitively sensitive to olaparib. In contrast, non-tumour cells have normally functioning double strand DNA break repair and are much less sensitive to olaparib driving an anti-tumour effect while sparing toxicity in healthy tissues. Olaparib is now FDA approved in ovarian cancer in patients with BRCA1 or BRCA2 mutated disease and who have received prior platinum-based therapy.

The combination of ceralasertib, an ATR inhibitor, and olaparib is attractive because olaparib generates RS, thereby creating dependency on the DNA damage response that is driven by ATR (Murai et al 2012, Pommier et al 2016). In patients with tumours that are aggressively dividing and may have underlying DNA repair defects, such as those with small cell lung cancer, the combination effect of ceralasertib and olaparib in generating anti-tumour activity is expected to be even greater, (McCabe et al 2006, Lord et al 2015, Lord et al 2008, Turner et al 2008, Bajrami et al 2014). CCI

CCI

CCI

2.2 Ceralasertib

Ceralasertib is a potent, selective inhibitor of the serine/threonine-specific protein kinase, ataxia telangiectasia and Rad3-related protein (ATR), with good selectivity against other phosphatidylinositol 3-kinase-related kinase (PIKK) family members (Foote et al 2013). This compound is being developed as an oral anti-tumour agent in patients with disease that is dependent upon ATR function for DNA repair; an example being tumours that are deficient of the serine/threonine-specific protein kinase, ataxia telangiectasia mutated (ATM). The focus of this study is to combine ceralasertib with olaparib, where the combination synergy

observed in human cancer models, can be tested in patients with small cell lung cancer who are resistant or refractory to 1st line platinum-based therapy.

Ceralasertib shows growth inhibition activity as monotherapy against multiple cancer cell lines in vitro, but showed strongest activity in haematological cell lines and those with deficiencies in the ATM signalling pathway, as determined by the inability to phosphorylate ATM on Ser1981 (autophosphorylation) or CHK2 on Thr68 (Foote et al 2015, Vendetti et al 2015, Kwok et al 2016, Yap et al 2016). For example, activity against ATM-pathway deficient LoVo (MRE11A mutant) cells is 0.44 µM compared to ATM-proficient HT-29 cells at 2.6 µM. The preferential cellular activity of ceralasertib against LoVo cells compared to HT-29 cells translated through to in vivo xenograft efficacy studies in nude mice. Ceralasertibwas active as a monotherapy *in vivo* with selective dose-dependent activity against LoVo xenografts with 81% TGI at 50 mg/kg PO once daily x14 days versus 10% growth inhibition against HT29 xenografts. These data indicate ceralasertib has enhanced growth inhibition activity against ATM-deficient tumours compared to ATM-proficient tumours as a monotherapy.

In addition to monotherapy activity, ATR inhibitors are also predicted to potentiate the activity of cytotoxic DNA damaging agents (through inhibition of ATR-dependent DNA repair processes) when used in combination. In *in vitro* combination studies against cancer cell lines, ceralasertibshowed good synergistic potentiation of the cytotoxic activities of DNA-damaging agents cisplatin, gemcitabine, melphalan and ionising radiation (IR) (see Investigator's Brochure). Combination studies against *in vivo* xenograft models in nude mice confirmed the *in vitro* findings with ceralasertib showing a dose-dependent, synergistic potentiation of Carboplatin or IR activity leading to enhanced growth inhibition and tumour regressions respectively.

2.3 Olaparib

Olaparib (AZD2281, KU-0059436, Lynparza) is a potent Polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerisation (PARP) inhibitor (PARP-1, -2 and -3) that is being developed as an oral therapy, both as a monotherapy (including maintenance) and for combination with chemotherapy and other anti-cancer agents. Olaparib has been approved for the following indications (wording from US prescribing information):

- the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in a complete or partial response to platinum-based chemotherapy.

- the treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza.

PARP inhibition is a novel approach to targeting tumours with deficiencies in DNA repair mechanisms. PARP enzymes are essential for repairing DNA single strand breaks (SSBs).

Inhibiting PARPs leads to the persistence of SSBs, which are then converted to the more serious DNA double strand breaks (DSBs) during the process of DNA replication. During the process of cell division, DSBs can be efficiently repaired in normal cells by homologous recombination repair (HR). CCI , such as ovarian cancers in patients with BRCA1/2 mutations, cannot accurately repair the DNA damage, which may become lethal to cells as it accumulates. In such tumour types, olaparib may offer a potentially efficacious and less toxic cancer treatment compared with currently available chemotherapy regimens.

BRCA1 and BRCA2 defective tumours are intrinsically sensitive to PARP inhibitors, both in tumour models in vivo (Rottenberg et al 2008, Hay et al 2009) and in the clinic (Fong et al 2009). The mechanism of action for olaparib results from the trapping of inactive PARP onto the single-strand breaks preventing their repair (Helleday 2011; Murai et al 2012). Persistence of SSBs during DNA replication results in their conversion into the more serious DNA DSBs that would normally be repaired by HR repair. Olaparib has been shown to inhibit selected tumour cell lines in vitro and in xenograft and primary explant models as well as in genetic BRCA knock-out models, either as a stand-alone treatment or in combination with established chemotherapies.

2.4 Rationale for study design, doses, and control groups

The rationale for the unmet medical need in refractory or resistant ED SCLC is described in Section 2.2.1 of the master protocol. The rationale for the specific study design aspects of Arm C is described below.

2.4.1 Ceralasertib in combination with olaparib

Tumor cells rely on cell cycle checkpoints for repair of DNA damage induced by cytotoxic and other agents. Olaparib inhibits the repair of single strand DNA breaks by trapping inactive PARP onto the DNA. While these single strand DNA breaks are converted into double strand DNA breaks during replication, they also cause replication stress (RS) triggering activation and dependence on ATR. As ceralasertib selectively inhibits ATR, it prevents stalling of replication forks and firing of new replication forks begins, causing cells to continue through S phase with incompletely replicated DNA, ultimately resulting in cell death through apoptosis. Non-clinical studies have demonstrated the synergy of ceralasertib+olaparib *in vitro* and *in vivo*, and early signs of the clinical benefit of the combination are becoming apparent in the ingoing clinical study (recenty presented at the joint EORTC-NCI-AACR conference) (Yap et al 2016).

2.4.2 Clinical experience with ceralasertib

CCI

- CCI

- CCI [redacted]

[redacted]

[redacted]

[redacted]

CCI [redacted]

CCI [redacted]

					CCI [redacted]

CCI [redacted]

CCI [redacted]

2.4.3 Ceralasertib pharmacokinetic and pharmacodynamic data

CCI [redacted]

CCI [redacted]

2.4.4 Clinical experience with olaparib

This section lists those ADRs that are currently regarded as expected for regulatory reporting purposes. A description of selected adverse reactions associated with olaparib are provided below. For full information on the 'Emerging safety profile' of olaparib and ceralasertib, refer to sections 5 and 6 of the respective IBs.

Olaparib monotherapy has been associated with laboratory findings and/or clinical diagnoses, generally of mild or moderate severity (CTCAE Grade 1 or 2) and generally not requiring treatment discontinuation.

The safety profile is based on pooled data from 1248 patients treated with olaparib monotherapy in clinical trials in the therapeutic indication at the recommended dose.

The following adverse reactions have been identified in completed clinical trials with patients receiving olaparib monotherapy where patient exposure is known.

Adverse Drug Reactions are organised by Medical Dictionary for Regulatory Activities (MedDRA) SOC and then by MedDRA preferred term in Appendix C Table 2. Within each SOC, preferred terms are arranged by decreasing frequency and then by decreasing seriousness. Frequencies of occurrence of adverse reactions are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1000); and very rare (<1/10,000) including isolated reports.

Appendix C Table 2 Adverse Drug Reactions reported in Clinical Trials with Olaparib

MedDRA SOC	MedDRA Term	CIOMS descriptor/ Overall Frequency (All CTCAE grades)	Frequency of CTCAE Grade 3 and above
Blood and lymphatic system disorders	Anaemia[a]	Very common	Very common
	Neutropenia[a]	Common	Common
	Thrombocytopenia[a]	Common	Common
	Leukopenia[a]	Common	Common
	Lymphopenia[a]	Uncommon	Uncommon
Immune system disorders	Rash[a]	Common	-
	Hypersensitivity[a]	Uncommon	-
	Dermatitis[a]	Uncommon	-
Metabolism and nutrition disorders	Decreased appetite	Very common	Uncommon
Nervous system disorders	Dizziness	Very common	Uncommon
	Headache	Very common	Uncommon
	Dysgeusia	Very common	-
Gastrointestinal disorders	Vomiting	Very common	Common
	Diarrhoea	Very common	Common
	Nausea	Very common	Common
	Dyspepsia	Very common	-
	Stomatitis	Common	Uncommon
	Upper abdominal pain	Common	Uncommon
General disorders	Fatigue (including asthenia)	Very common	Common
Investigations	Increase in creatinine	Common	Uncommon
	Mean corpuscular volume elevation	Uncommon	-

a Anaemia includes PTs of anaemia, haemoglobin decreased, red blood cell count decreased, and haematocrit decreased; Neutropenia includes PTs of neutropenia, granulocytopenia, granulocyte count decreased and neutrophil count decreased, febrile neutropenia and neutropenic sepsis; Thrombocytopenia includes PTs of thrombocytopenia, platelet count decreased and plateletcrit decreased; Leukopenia includes PTs of leukopenia and white blood cell count decreased; Rash includes PTs of rash, rash erythematous, rash generalised, rash macular, rash maculo-papular, rash papular, rash pruritic, exfoliative rash and generalised erythema; Hypersensitivity includes PTs of hypersensitivity and drug hypersensitivity; Dermatitis includes PTs of dermatitis, dermatitis allergic and dermatitis. CIOMS Council for International Organizations of Medical Sciences; CTCAE Common Terminology Criteria for Adverse Events v.3.0; MedDRA Medical Dictionary for Regulatory Activities; SOC System organ class.

2.4.4.1 Description of selected adverse reactions associated with olaparib monotherapy

Haematological toxicity

Anaemia and other haematological toxicities are generally low grade (CTCAE Grade 1 or 2), however, there are reports of CTCAE Grade 3 and higher events. Anaemia was the most common CTCAE Grade ≥3 adverse reaction reported in clinical studies with first onset generally reported in the first 3 months of treatment. An exposure-response relationship between olaparib and decreases in haemoglobin has been demonstrated. In clinical studies with olaparib, the incidence of CTCAE Grade ≥2 shifts (decreases) from baseline in haemoglobin was 20%, absolute neutrophils 15%, platelets 5%, lymphocytes 30% and leucocytes 20% (all % approximate).

The incidence of elevations in MCV from low to normal at baseline to above the upper limit of normal was approximately 55%. Levels appeared to return to normal after treatment discontinuation and did not appear to have any clinical consequences.

Baseline testing, followed by monthly monitoring of complete blood counts is recommended for the first 12 months of treatment with olaparib, and periodically after this time to monitor for clinically significant changes in any parameter during treatment which may require dose interruption or reduction and/or further treatment.

Other laboratory findings

In clinical studies with olaparib the incidence of CTCAE Grade ≥2 shifts (elevations) from baseline in blood creatinine was approximately 15%. Data from a double-blind placebo controlled study showed median increase up to 23% from baseline remaining consistent over time and returning to baseline after treatment discontinuation, with no apparent clinical sequelae; 90% of patients had creatinine values of CTCAE Grade 0 at baseline and 10% were CTCAE Grade 1 at baseline.

Nausea and vomiting

Nausea was generally reported very early, with first onset within the first month of olaparib treatment in the majority of patients. Vomiting was reported early, with first onset within the first two months of olaparib treatment in the majority of patients. Both nausea and vomiting were reported to be intermittent for the majority of patients.

Combination studies

Safety data from studies in which olaparib has been administered in combination with other agents are discussed in Section 2.5. The degree of bone marrow suppression observed in some patients in the combination studies has however been greater than would be expected with the chemotherapy agent alone, as per label information. Myelotoxicity has been observed in studies evaluating olaparib with the following combination therapies: DTIC; carboplatin;

paclitaxel; carboplatin + paclitaxel; gemcitabine; topotecan; cisplatin; doxorubicin, cisplatin + gemcitabine; or irinotecan.

The principal haematological toxicities observed have been neutropenia, thrombocytopenia and anaemia. These findings are consistent with pre-clinical findings (Delaney et al 2000, Evers et al 2008, Menear et al 2008, Miknyoczki et al 2003, and Rottenberg et al 2008).

2.4.4.2 Adverse events of special interest for olaparib

Myelodysplastic syndrome/acute myeloid leukaemia

The incidence of MDS/AML in patients treated in clinical trials with olaparib monotherapy, including long-term survival follow-up, was <1.5% and the majority of events had a fatal outcome. All patients had potential contributing factors for the development of MDS/AML, having received previous chemotherapy with platinum agents. Many had also received other DNA damaging treatments. The majority of reports were in germline BRCA mutation carriers and some of the patients had a history of previous cancer or of bone marrow dysplasia. If MDS and/or AML are confirmed while on treatment with olaparib, it is recommended that olaparib should be discontinued and the patient be treated appropriately.

New Primary Malignancies other than MDS/AML

New primary malignancies have been reported in <1% of patients. There were other contributing factors/potential alternative explanations for the development of the new primary malignancy in all cases, including documented BRCA mutation, treatment with radiotherapy and extensive previous chemotherapy including carboplatin, taxanes, anthracyclines and other alkylating and DNA damaging agents.

Pneumonitis

Pneumonitis has been reported in <1.0% patients treated with olaparib monotherapy in clinical studies. Reports of pneumonitis had no consistent clinical pattern and were confounded by a number of pre-disposing factors (cancer and/or metastases in lungs, underlying pulmonary disease, smoking history, and/or previous chemotherapy and radiotherapy). When olaparib was used in clinical studies in combination with other therapies there have been events with a fatal outcome. If patients present with new or worsening respiratory symptoms such as dyspnoea, cough and fever, or an abnormal chest radiologic finding is observed, olaparib treatment should be interrupted and prompt investigation initiated. If pneumonitis is confirmed, olaparib treatment should be discontinued and the patient treated appropriately.

2.4.5 Ceralasertib + olaparib combination therapy dose rationale

The combination of olaparib and ceralasertib has been administered to 59 patients with advanced malignancy with the goal of establishing the dosing schedule. The recommended phase 2 dose was established as 160 mg QD ceralasertib days 1-7 in combination with 300 mg BID olaparib on a 28 day cycle. The dosing schedule of olaparib (300mg twice daily each day) is the same as the licensed dose.

The dosing schedule of ceralasertib was supported by the PK-PD model of thrombocytopenia, predicting a period of 21 days free of drug to achieve a full platelet recovery. The recommended dose 160 mg QD was predicted to maintain ceralasertib mean steady state concentrations above the estimated IC90 threshold (based on ATR enzyme inhibition assay in LoVo cells) and the GI90 threshold (based on the cellular growth inhibition activity in LoVo cells) across the full dosing interval i.e 24 h. Please refer to ceralasertib IB for further information around the *in-vitro* threshold values. In addition, this daily dose level was associated with a decrease in peripheral monocytes in most of the patients and the preliminary blood cell count data from D5330C00004 and D5330C00002 studies suggested this decrease to be ceralasertib specific and dose dependent (monocyte decrease was not observed with either single agent olaparib or durvalumab. Monocytes have been characterized as being deficient in DNA base excision repair and PARP1 expression (Bauer et al 2011), suggesting an on-target synthetic lethal effect of ceralasertib mediated ATR inhibition in this cell type. Utilizing the monocyte decrease as a quantitative measure of ceralasertib pharmacological activity, the recommended Phase 2 dose of 160mg QD D1-7 was driven by maintaining maximally active exposure consistent with manageable safety.

2.4.6 Rationale for study endpoints

The rationale for study endpoints is provided in Section 2.2.3 of the master protocol.

2.5 Benefit/risk and ethical assessment

The unmet need in refractory or resistant ED SCLC is described in Sections 2.1 and 2.3 of the master protocol. Additional information on the potential benefits of each agent (ceralasertib and olaparib) and an assessment of the potential and known risks can also be found in the current IBs. Specific information relating to ceralasertib and olaparib is summarized below.

2.5.1 Potential benefits

2.5.1.1 Ceralasertib

CCI

2.5.1.2 Olaparib

Olaparib was first approved by the FDA as a capsule formulation (400 mg twice daily) for the treatment of women with BRCA-positive advanced ovarian cancer following treatment with 3 or more prior lines of chemotherapy. The new drug application (NDA) for olaparib tablets was granted FDA priority review as a maintenance therapy in relapsed patients with platinum-sensitive ovarian cancer. These are the current licensed indications for olaparib:

- For the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, who are in complete or partial response to platinum-based chemotherapy
- For the treatment of adult patients with deleterious or suspected deleterious germline *BRCA*-mutated advanced ovarian cancer who have been treated with 3 or more prior lines of chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for LYNPARZA

2.5.1.3 Ceralasertib + olaparib

Ceralasertib in combination with olaparib is considered to have a positive benefit-risk profile for all patients with advanced cancer. Pre-clinical data suggest that olaparib synergises with ceralasertib to drive tumour regressions in a range of human cancers, irrespective of BRCA mutation status. Where tumour cells are dependent upon ATR for DNA repair through defects in HR or other DNA repair pathways e.g. ATM mutations, ceralasertib will increase tumour sensitivity to olaparib therapy; however, an effect in tumour cells that are proficient in DNA repair may also occur and therefore this study has been designed to allow the potential for assessment of efficacy across allcomers with ED-SCLC.

2.5.2 Identified and potential risks

2.5.2.1 Ceralasertib

As of 17th July 2017, no ceralasertib monotherapy studies have been completed, and ceralasertib has been administered to approximately 49 subjects as monotherapy in ongoing studies D5330C00001, D5330C00004 and D5330C00002. Thrombocytopenia and anemia are considered expected events when ceralasertib has been given as monotherapy and haematological toxicities (thromobocytopenia, neutropenia and anaemia) when ceralasertib has been given in combination with other myelosuppressive agents. Anaemia and fatigue are

very common across the programme. Overall, such events were predictable from pre-clinical data and from what is known about the mechanism of action of ceralasertib and the combination drug olaparib. The observed toxicities in the clinical setting have been manageable with standard practice. None of the events have been fatal.

No reproductive toxicology nor teratogenic studies have been conducted with ceralasertib to date, and it is unknown whether the drug is excreted in human milk. Therefore, women of childbearing potential and men should agree to use adequate contraception prior to commencing study treatment and for the duration of study participation and women who are breast feeeding are excluded from the study. Both women and men should be fully informed of the lack of reproductive toxicity testing, and women must have a negative pregnancy test prior to enrolment.

Please refer to Section 5.4 'emerging safety profile'of the current ceralasertib IB for complete list of events considered as identified risks, and Section 6 of IB 'summary of data and guidance to investigators' for information on the potential risks and risk mitigation strategy.

2.5.2.2 Olaparib

Adverse laboratory findings and/or clinical diagnoses considered to be associated with administration of olaparib monotherapy include haematological effects (anaemia, neutropenia, lymphopenia, thrombocytopenia, MCV elevation and increase in blood creatinine), nausea and vomiting, decreased appetite, diarrhoea, dyspepsia, stomatitis, upper abdominal pain, dysgeusia, fatigue (including asthenia), headache and dizziness. Most of these events were generally mild or moderate in intensity.

In a relatively small number of patients, pneumonitis, MDS/AML and new primary malignancies have been observed. Evidence from across the development programme for olaparib does not support a conclusion that there is a causal relationship between olaparib and these events. These are important potential risks for olaparib and are being kept under close surveillance.

See the latest version of the IB for further information.

2.5.2.3 Ceralasertib + olaparib

See Section 2.4 for clinical experience with ceralasertib and olaparib. A number of potential safety signals have been identified on the basis of general toxicology, safety pharmacology, genotoxicity and clinical studies, which were predictable from pre-clinical studies and the mode of action of ceralasertib. Most of these signals have not been confirmed to be causally related to ceralasertib; some are considered potential risks which are being monitored in ongoing clinical trials e.g. gastrointestinal toxicity, hepatic toxicity. The principal risk associated with the ceralasertib + olaparib combination is exacerbation of haematologic toxicity which is considered an Adverse Drug Reaction or identified risk for ceralasertib. In addition, some clinical toxicities from ceralasertib overlap with those seen with olaparib use in humans e.g. anaemia, neutropenia, leukopenia, thrombocytopenia of potential prolonged duration. A small number of patients have been exposed to the combination, and a tolerable dose and schedule

has been reached. Risk minimisation and detailed toxicity management guidelines are incorporated in the current protocol and the sponsor will continued to monitor the clinical and nonclinical data for emerging safety information. The risks are manageable within current clinical practice with the measures already in place and do not change the benefit / risk profile for ceralasertib in the ongoing and planned clinical studies.

2.5.2.4 Summary benefit:risk statement

The safety profile of ceralasertib when combined with olaparib has been shown to be acceptable, and ceralasertib has shown activity in several tumor types in the clinical development program to date. Considering the measures taken to minimse risk to patients participating in the Phase I and II clinical studies, the identified and potential risks associated with ceralasertib in combination with olaparib are justified by the anticipated benefits that may be afforded to patients with relapsed SCLC. The overall benefit-risk evaluation supports the investigation of oral ceralasertib and olaparib in patients with platinum resistant and refractory ED-SCLC according to this clinical protocol.

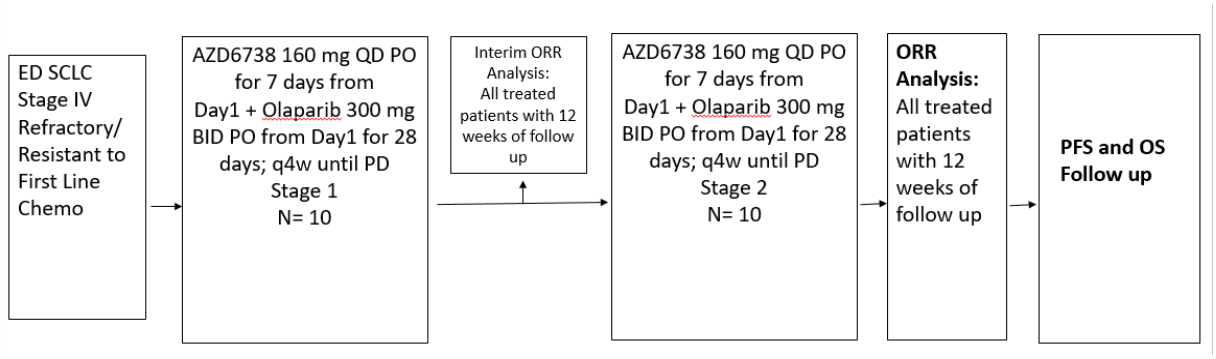
3. STUDY DESIGN

Arm C will investigate the preliminary efficacy, safety, and tolerability of ceralasertib in combination with olaparib (both given PO) to patients who progress during first-line chemotherapy (platinum refractory) or those who progress within 90 days after completing first-line chemotherapy (platinum resistant) and have not received further treatment apart from first-line platinum-based chemotherapy. Patients should be enrolled within 90 days of progression in order to be accepted into the study.

For Arm C, up to 20 eligible patients will be treated, and all patients will receive:

- ceralasertib 160 mg QD days 1-7 + olaparib 300 mg BID days 1-28; every 4 weeks (q4w)

Appendix C Figure 2 Study design



QD once daily; ED-SCLC Extensive-stage disease small-cell lung cancer; ORR Objective response rate; OS Overall survival; PFS Progression-free survival; PD Progression Disease PO By mouth; q4w Every 4 weeks.

4. STUDY OBJECTIVES

4.1 Primary objective

See Section 3.1 of the master protocol.

4.2 Secondary objectives

See Section 3.2 of the master protocol.

4.3 Safety objectives

4.4 Exploratory objectives

See Section 3.4 of the master protocol.

5. PATIENT SELECTION, ENROLLMENT, RANDOMIZATION, RESTRICTIONS, DISCONTINUATION, AND WITHDRAWAL

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

5.1 Inclusion criteria

The complete set of inclusion criteria applicable to Arm C are described in this section. Patients should fulfil all inclusion criteria to to enter the study:

1. Male or female ≥18 years at the time of screening.

2. Ability to swallow and retain oral medication

3. Written informed consent and any locally required authorization (eg, Health Insurance Portability and Accountability Act in the US, EU Data Privacy Directive in the EU) obtained from the patient/legal representative prior to performing any protocol-related procedures, including screening evaluations.

4. Histologically or cytologically documented extensive disease American Joint Committee on Cancer Stage IV SCLC (T any, N any, M1 a/b) at initial diagnosis, also including patients with:

- T3-4 due to multiple lung nodules that are too extensive or have tumor/nodal volume that is too large to be encompassed in a tolerable radiation plan.
- Biopsy-proven mixed SCLC and NSCLC histology
- Brain metastases; must be asymptomatic or treated and stable off steroids and anti-convulsants for at least 1 month prior to study treatment. Patients with suspected brain metastases at screening should have a computed tomography (CT)/magnetic resonance imaging (MRI) of the brain prior to study entry.

5. Patients must have demonstrated progressive disease (PD) either during first-line platinum-based chemotherapy (platinum refractory) or within 90 days of completing platinum-based chemotherapy (platinum resistant), and have not received further treatment apart from first-line platinum-based chemotherapy. Patients should be enrolled within 90 days of progression in order to be accepted into the study.

6. World Health Organization (WHO)/Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-1.

7. At least 1 lesion, not previously irradiated, that can be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes, which must have a short axis ≥15 mm) with CT or MRI and that is suitable for accurate repeated measurements as per RECIST 1.1 guidelines.

8. Willingness and ability to comply with study and follow up procedures.

9. Life expectancy of at least 8 weeks.

10. Patients must have adequate organ and bone marrow function measured within 28 days prior to treatment as defined below:
Haemoglobin (Hb) ≥ 10.0 g/dL with no blood transfusions (packed red blood cells) in the past 28 days

- Absolute neutrophil count (ANC) ≥1.5 x 10^9 / L without the use of G-CSF
- Platelet count ≥ 100 x 109/L with no platelet transfusion in the past 28 days
- Total bilirubin ≤ 1.5 x institutional upper limit or normal (ULN) unless the patient has documented Gilbert's Syndrome
- Aspartate aminotransferase (AST) / alanine aminotransferase (ALT) ≤ 2.5 x institutional ULN unless liver metastases are present in which case they must be ≤ 5 x ULN

- Patients must have a creatinine clearance (CrCl) estimated using the Cockcroft-Gault equation of ≥ 51 mL/min:

$$\text{Estimated CrCl} = \frac{(140 - age[years])\ x\ weight\ (kg)\ x\ (F)a}{serum\ creatinine\ (mg/dL)\ x72}$$

[a] where F=0.85 for females and F=1 for males

11. Evidence of post-menopausal status or negative urinary or serum pregnancy test for female pre-menopausal patients. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

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

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

12. Women of childbearing potential and their partners, who are sexually active, must agree to the use of 2 highly effective forms of contraception in combination from the signing of the informed consent, through the period of taking study treatment and for at least 1 month after last dose of study drug (s), or they must totally / truly abstrain from any form of sexual intercourse (as described in Appendix G).

13. Male patients must use a condom during treatment and for 6 months after the last dose of study drug(s) when having sexual intercourse with a pregnant woman or with a woman of childbearing potential. Female partners of male patients should also use a highly effective form of contraception (see Appendix G) for 6 months after the last dose of study drug(s) if they are of childbearing potential.

5.2 Exclusion criteria

The complete set of exclusion criteria applicable to Arm C are described in this section. Patients should not enter the study if any of the following exclusion criteria are fulfilled:

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

2. Previous enrollment in the present study.

3. Participation in another clinical study with an investigational product (IP) during the last 4 weeks.

4. Concurrent enrollment in another clinical study unless it is an observational (non-interventional) clinical study or the follow-up period of an interventional study.

5. Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of IP. Note: Local surgery of isolated lesions for palliative intent is acceptable where this does not affect assessment of target lesions.

6. Any condition that, in the opinion of the Investigator, would interfere with the evaluation of the IP or interpretation of patient safety or study results. This includes but is not limited to: ongoing or active infection, including any patient known to have hepatitis B, hepatitis C and human immunodeficiency virus (HIV), any evidence of severe or uncontrolled systemic diseases e.g. symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, severe COPD, severe Parkinson's disease, active inflammatory bowel disease; active bleeding diatheses, renal transplant or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs from the study medications, or compromise the ability of the patient to give written informed consent. Screening for chronic conditions is not required.

7. Past medical history of interstitial lung disease, drug-induced pneumonitis, radiation pneumonitis that required steroid treatment, or any evidence of clinically active interstitial lung disease.

8. History of hypersensitivity to active or inactive excipients of any investigational drug in the study or drugs with a similar chemical structure or class to those investigated in the study.

9. History of another primary malignancy except for:

    - Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of study drug and of low potential risk for recurrence

    - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease

    - Adequately treated carcinoma in situ without evidence of disease (eg, cervical cancer in situ)

10. History of leptomeningeal carcinomatosis.

11. A diagnosis of ataxia telangiectasia

12. Cytotoxic chemotherapy within 21 days of Cycle 1 Day 1 is not permitted (a shorter duration of five half times is allowed for patients treated with non-cytotoxic drugs). Exposure to a small molecule IP within 30 days or 5 half-lives (whichever is longer) prior to Cycle 1 Day 1. The minimum washout period for immunotherapy is 42 days.

13. Previous treatment with a PARP inhibitor (including olaparib) or ATR inhibitor.

14. With the exception of alopecia, any unresolved toxicities from prior therapy ≥ Common Terminology Criteria for Adverse Events (CTCAE) grade 2. Patients with Grade ≥2 neuropathy will be evaluated on a case-by-case basis after consultation with AstraZeneca Study Physician

15. Spinal cord compression or brain metastases unless asymptomatic, stable and not requiring steroids for at least 4 weeks prior to start of study treatment

16. Concomitant use of known strong CYP3A inhibitors (eg. itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (eg. ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil). See Appendix I Disallowed Medications and Medications to be Administered with Caution for list of CYP3A inhibitors. The required washout period prior to starting study treatment is 2 weeks.

17. Concomitant use of known strong (e.g. phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) or moderate CYP3A inducers (e.g. bosentan, efavirenz, modafinil). See Appendix I Disallowed Medications and Medications to be Administered with Caution for list of CYP3A inducers. The required washout period prior to starting study treatment is 5 weeks for enzalutamide or phenobarbital and 3 weeks for other agents. Patients should stop using herbal remedies 7 days prior to the first dose of study medication and for the duration ot the trial.

18. Persisting (> 4 weeks) severe pancytopenia due to previous therapy rather than disease (ANC < 0.5 x 10^9/L or platelets < 50 x 10^9/L)

19. Cardiac dysfunction as defined as: Myocardial infarction within six months of study entry, NYHA Class II/III/IV heart failure, unstable angina, unstable cardiac arrhythmias or known reduced LVEF < 55%

20. Any of the following cardiac criteria:

- Mean resting corrected QT interval (QTc) >470 msec obtained from 3 electrocardiograms (ECGs) in 24 hours using the Fredericia formula
- Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG (e.g., complete left bundle branch block, third degree heart block)
- Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalaemia, congenital long QT syndrome, immediate family history of long QT syndrome or unexplained sudden death under 40 years of age
- Patients at risk of brain perfusion problems, e.g., carotid stenosis
- Patients with relative hypotension (< 100/60 mm Hg) or clinically relevant orthostatic hypotension, including a fall in blood pressure of >20mm Hg
- Uncontrolled hypertension requiring clinical intervention

21. Refractory nausea and vomiting, chronic gastrointestinal diseases or previous significant bowel resection, with clinically significant sequelae that would preclude adequate absorption of ceralasertib or olaparib.

22. Patients with uncontrolled seizures.

23. Judgment by the Investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions and requirements.

24. Radiation therapy to the chest and whole-brain irradiation must be completed at least 4 weeks prior to start of study treatment, and patients must have recovered from any acute adverse effects prior to start of study treatment. An exception to this is palliative radiotherapy with a limited field of radiation for palliation, which must be completed before the first dose of study treatment. In the case of palliative radiation to more than 30% of the bone marrow or with a wide field of radiation this must also be completed at least 4 weeks prior to the first dose of study medication.

25. Intestinal obstruction or CTCAE grade 3 or grade 4 upper GI bleeding within 4 weeks before the dosing.

26. Patients with myelodysplastic syndrome/acute myeloid leukaemia or with features suggestive of MDS/AML.

27. Whole blood transfusions in the last 120 days prior to entry to the study (packed red blood cells and platelet transfusions are acceptable up to 28 days prior to commencing study drugs).

28. Pregnant females, female patients who are breast-feeding or male or female patients of reproductive potential who are not employing an effective method of birth control.

29. Persistent toxicities (> or = CTCAE grade 2) caused by previous cancer therapy, excluding alopecia and CTCAE grade 2 peripheral neuropathy.

5.3 Patient enrollment and randomization

See Section 4.3 of the master protocol.

5.3.1 Procedures for handling incorrectly enrolled or randomized patients

See Section 4.4 of the master protocol.

5.4 Methods for assigning treatment groups

Not Applicable.

5.5 Restrictions

5.5.1 Food Restrictions

It is not recommended to consume grapefruit juice while on olaparib therapy. When ceralasertib is administered in combination with olaparib, patients must fast as directed for at least 2 hours prior to the dosing and for at least 1 hour after the dose. When olaparib is given on its own, the olaparib tablet formulation can be given without regard to food.

5.5.2 Foetal risk

Olaparib is regarded as a compound with medium/high foetal risk. Women of childbearing potential (WoCBP) and their partners, who are sexually active, must agree to the use of TWO highly effective forms of contraception in combination throughout the period of taking study treatment and for at least 1 month after last dose of study drug(s), or they must totally/truly abstain from any form of sexual intercourse (see below).

Male patients and their partners, who are sexually active and of childbearing potential, must agree to the use of TWO highly effective forms of contraception in combination, throughout the period of taking study treatment and for 6 months after last dose of study drug(s) due to the unknown effects of the study drug on the sperm, or they must totally/truly abstain from any form of sexual intercourse (see below). Male patients should not donate sperm throughout the period of taking study treatment and for 6 months following the last dose of study drug(s).

For definitions and lists of acceptable non-hormonal and hormonal birth control methods see Appendix G Definition of Women of Childbearing Potential and Acceptable Contraceptive Methods**.**

5.5.3 Concomitant treatments

Other medication other than that described above, which is considered necessary for the patient's safety and well-being, may be given at the discretion of the Investigator and recorded in the appropriate sections of the Case Report Form. In addition, any unplanned diagnostic, therapeutic or surgical procedure performed during the study period must be recorded in the CRF. Patients must comply with the concomitant treatment information described in the core study protocol and those described in the olaparib Investigators' Brochure.

5.5.3.1 Women of childbearing potential

Women of childbearing potential (WoCBP) may be included only if acceptable contraception is in place for 2 weeks before commencing study treatment for the duration of the study, and for 1month after the last dose of study drug. Women of childbearing potential and their partners, who are sexually active, must agree to the use of TWO highly effective forms of contraception in combination (see Appendix G Definition of Childbearing Potential and Acceptable Contraceptive Methods), throughout the period of taking study treatment and for at least 1 month after last dose of study drug(s), or they must totally/truly abstain from any form of sexual intercourse. Contraceptives that are prone to drug-drug interactions may not be effective due to a potential CYP3A4 interaction with ceralasertib.

All WoCBP must have a negative pregnancy test during screening and within 3 days prior to starting each treatment cycle.

Male patients who are involved in the study must agree to avoid procreative and unprotected sex (ie, using acceptable forms of contraception as described in Appendix G) and must not donate sperm during the study and for 6 months after the last dose of study drug. Where the female partner is pregnant or not using effective birth control, men should be advised to abstain while in the study and for 6 months after the last dose of study drug.

Female partners, who are of childbearing potential, of men participating in the study will also be required to use effective contraceptive measures (detailed in Appendix G) while their partner is on study drug and for 6 months thereafter.

5.5.4 Photosensitivity

Patients are advised to take precautions when outside in the sun, e.g., limiting the duration of sun exposure, wearing protective clothing (hat and sunglasses) and sunscreen

5.6 Discontinuation of investigational product

See Section 4.9 of the master protocol.

5.7 Criteria for withdrawal

See Section 4.10 of the master protocol.

5.8 Discontinuation of the study

See Section 4.11 of the master protocol.

6. STUDY PLAN AND TIMING OF PROCEDURES

The procedures for the screening and the treatment periods in this study are presented in Appendix C Table 3 Schedule of assessment for olaparib + ceralasertib (AZD6738) combination therapy

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Appendix C Table 3 Schedule of assessment for olaparib + ceralasertib (AZD6738) combination therapy

		Screening	Cycle 1			Subsequent on treatment visits (every 28 days)	Study treatment discontinued	30-day follow-up after last dose of study medication	Follow up for progression and survival	Details in section
Visit Number			**2**	**3**	**4**	**Visit No.5 onwards**				
Day		**-28 to -1**	**1**	**7**	**15**	**Cycle X, Day 1**			**Every 8 weeks[n]**	
Visit Window					**± 3d**	**up to 3 days prior to CXD1**	**up to 7 days after discontinuation**	**± 7d**	**± 7d**	
Informed consent		X								Appendix C section 6.1
Optional Informed consent for Optional exploratory genetic sample		X								Appendix C section 7.4.5
Optional Informed consent for Tumor Biopsy		X								Appendix C section 6.1
Medical / surgical history[a]		X								Appendix C section 6.1
Demographics		X								Appendix C section 6.1
Smoking consumption		X								Appendix C section 6.1
Inclusion/ Exclusion criteria		X								Appendix C sections 5.1 and 5.2
Concomitant medications including blood transfusions		X	X	X	X	X	X	X		Section 8.7 of master protocol and Appendix C sections 5.5and 9.7

		Screening	Cycle 1			Subsequent on treatment visits (every 28 days)	Study treatment discontinued	30-day follow-up after last dose of study medication	Follow up for progression and survival	Details in section
Visit Number			**2**	**3**	**4**	**Visit No.5 onwards**				
Day		**-28 to -1**	**1**	**7**	**15**	**Cycle X, Day 1**			**Every 8 weeks[n]**	
Visit Window					**± 3d**	**up to 3 days prior to CXD1**	**up to 7 days after discontinuation**	**± 7d**	**± 7d**	
Adverse events[b]		X	X	X	X	X	X	X		Section 7 of master protocol and Appendix C section 8
Vital signs (BP, pulse and temperature)		X	X			X	X	X		Section 6.2.4 of master protocol and Appendix C section 7.1.2
Physical examination and weight[c]		X	X			X	X	X		Section 6.2.2 of master protocol and Appendix C section 7.1.1
ECOG performance status		X	X			X	X			Section 6.3.1 of master protocol and Appendix C section 7.1.1
Pregnancy test[d]		X	X			X		X		Section 6.2.1 of master protocol
Triplicate ECG[e]		X	X	X		X	X			Section 6.2.3 of master protocol and Appendix C section 7.1.3
Haematology, coagulation, chemistry and urinalysis[f]		X	X	X	X	X[f]	X	X		Section 7.1.4 of Appendix C

		Screening	Cycle 1			Subsequent on treatment visits (every 28 days)	Study treatment discontinued	30-day follow-up after last dose of study medication	Follow up for progression and survival	Details in section
Visit Number			**2**	**3**	**4**	**Visit No.5 onwards**				
Day		**-28 to -1**	**1**	**7**	**15**	**Cycle X, Day 1**			**Every 8 weeks[n]**	
Visit Window					**± 3d**	**up to 3 days prior to CXD1**	**up to 7 days after discontinuation**	**± 7d**	**± 7d**	
Hepatitis B, C and HIV		X								Section 6.3.2. of master protocol
Blood sample for Cytokines			X	X	X	X	X[m]			Section 7.4.1 and 7.4.2 of Appendix C
PK analysis[g]			X	X		Cycles 2 to 6 only				Section 6.4 of master protocol and Appendix C section 7.2
Blood samples for biomarker analysis: plasma and PBMCs isolated from whole blood			X	X	X	X	X[m]			Section 6.6 of master protocol
Peripheral blood for CCI			X			X	X[m]			Section 6.6.1.3of master protocol and Appendix C section 7.4.1
Peripheral blood for CCI			X		X		X[m]			Sections 6.6.1.2 and 6.6.1.3 of master protocol and Appendix C section 7.4.2
mRNA			X							Appendix C section 7.4.1

		Screening	Cycle 1			Subsequent on treatment visits (every 28 days)	Study treatment discontinued	30-day follow-up after last dose of study medication	Follow up for progression and survival	Details in section
Visit Number			**2**	**3**	**4**	**Visit No.5 onwards**				
Day		**-28 to -1**	**1**	**7**	**15**	**Cycle X, Day 1**			**Every 8 weeks[n]**	
Visit Window					**± 3d**	**up to 3 days prior to CXD1**	**up to 7 days after discontinuation**	**± 7d**	**± 7d**	
Tumour assessment (RECIST 1.1)[h]		X	First scan at 8 weeks, then 4 weeks later (i.e. at 12 weeks) and then every 8 weeks (all ± 1 week), from the first day of investigational drug administration for the first 72 weeks, then every 12 weeks ± 1 week hereafter, until disease progression.							Section 6.1 of master protocol
Archival tissue (if availaible)[i]		X								Appendix C Section 7.4.3
Tumour biopsy with biomarker analyses (optional)[j]		X		X			X[m]			Appendix C Section 7.4.4
Optional exploratory genetic sample (optional)		X								Appendix C Section 7.4.5
Ceralasertib and olaparib dispensing			X			X				Appendix C Section 9
Dispense/review/collect Dosing Diary[k]			X	X	X	X				Appendix C Section 9
Dosing with ceralasertib[l]			Dosing once daily on Days 1-7 only							Appendix C sections 9.1.1. and 9.2
Dosing with olaparib[l]			Continuous twice daily dosing							Appendix C sections 9.1.2 and 9.2
Post discontinuation anticancer therapy[o]									X	NA

		Screening	Cycle 1			Subsequent on treatment visits (every 28 days)	Study treatment discontinued	30-day follow-up after last dose of study medication	Follow up for progression and survival	Details in section
Visit Number			**2**	**3**	**4**	**Visit No.5 onwards**				
Day		**-28 to -1**	**1**	**7**	**15**	**Cycle X, Day 1**			**Every 8 weeks[n]**	
Visit Window					**± 3d**	**up to 3 days prior to CXD1**	**up to 7 days after discontinuation**	**± 7d**	**± 7d**	
Survival status									X	Section 6.1.1 of master protocol

a This should include any previous cancer therapies (including radiotherapy and respond to current chemotherapy regimen) as well as any history of blood transfusion 120 days prior to entry to the sudy, with reasons (e.g. bleeding or myelosuppression).
b All ongoing AEs/ SAEs and any new AEs / SAEs identified during the 30 calendar day's follow-up period after last dose of study medication must be followed up to resolution.
c Physical examination should be done as per schedule but does not need to be recorded in the eCRF after the baseline assessment (except for weight which should be collected at each visit). Any clinically significant changes not unequivocally related to disease progression should be recorded as AEs.Height will be measured at screening only.
d Pregnancy tests using blood or urine samples will be performed for women of childbearing potential within 28 days prior to the start of study treatment, on Day 1 of the study prior to commencing treatment, on Day 1 of each subsequent cycle and at the follow-up visit 30 days after last dose of study medication. If results are positive, the patient must be discontinued from the study treatment immediately. Tests will be performed by the hospital's local laboratory.
e Triplicate ECG is required within 7 days prior to starting study treatment. All ECG assessments to be done in triplicate pre-dose on Cycle 1 Day 1 (additional baseline), within 1-2 hours of dosing on Day 7 of cycle 1, and Day 1 of every subsequent cycle, and on discontinuation of study treatment.
f Lab tests include FBC, Coagulation, Clinical Chemistry, CRP, urinalysis (coagulation test and urinalysis should be performed at screening and only if clinically indicated thereafter). Safety blood samples should be assessed prior to starting a new cycle, ideally on the day dosing is planned, but within 3 days prior to dosing will be acceptable.
g A common PK time window will be used for olaparib and ceralasertib in all patients: Cycle 1 Day 1: 1-3 hours, 3-6 hours and 6-12 hours post-dosing, Cycle 1 Day 7: pre-dose, 0.5-1 hour, 1-3 hours, 3-6 hours and 6-12 hours post-dosing, and Cycle X Day 1: single sample at 1-6 hours post-dosing only
h RECIST 1.1 assessments will be performed on images from CT (preferred) or MRI, each preferably with IV contrast of the chest, abdomen (including liver and adrenal glands), and pelvis. Pelvic imaging is recommended only when primary or metastatic disease in the pelvic region is likely. Additional anatomy should be imaged based on signs and symptoms of individual patients at baseline and follow-up. Baseline assessments should be performed no more than 28 days before the date of enrollment and, ideally, should be performed as close as possible to and prior to the start of the initial dose of IP. If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their next scheduled visit.
i Archival tissue collection if available, ideally 10 x 5 µm sections for sequencing
j Optional biopsy can be taken in Cycle 1 between day 3 and day 8, up to 24 hours after the last dose of ceralasertib in that cycle. At study treatment discontinuation, the biopsy can be taken between 0 and 96 hrs post last dose.
k Review ceralasertib and olaparib dosing compliance with the patient at the beginning of each new treatment cycle when study drug is dispensed.
l Ceralasertib should be taken with approximately 8 ounces of water. When ceralasertib is administered in combination with olaparib, patients must fast for at least 2 hours prior to the dosing and for at least 1 hour after the dose. When olaparib is given on its own, the olaparib tablet formulation can be given without regard to food. Please note that the cycle length for ceralasertib + olaparib and olaparib monotherapy will be 28 days.

m Progression only

n Following treatment discontinuation, assessments for survival must be made monthly for the first 3 months and then every 2 months thereafter.

o Details of any treatment for SCLC (including surgery) post the last dose of IP must be recorded in the eCRF. At minimum, collect the start date and description of the subsequent anticancer therapy.

Note: All assessments on treatment days are to be performed prior to dosing, unless otherwise indicated.

6.1 Enrollment/screening period

All screening and enrollment procedures will be performed according to the assessment schedule in Appendix C Table 3 Schedule of assessment for olaparib + ceralasertib (AZD6738) combination therapy

. Demographic data and other characteristics will be recorded including date of birth or age, gender, smoking history, and race/ethnicity, according to local regulations. A standard medical and surgical history will be obtained.

Written informed consent and any locally required privacy act document authorization must be obtained prior to performing any protocol specific procedures, including screening/baseline evaluations. Optional informed consent for paired biopsies will also be obtained. If laboratory or imaging procedures were performed for other reasons prior to signing consent, these can be used for screening purposes with consent of the patient. However, all screening laboratory and imaging results must have been obtained within 28 days of enrollment. All patients will have the option to provide consent to supply a sample of their tumor (archived or newly acquired biopsy) for entry into this study. This consent is included in the main patient informed consent form.

Screening/baseline evaluations may be performed over more than 1 visit.

The timing of vital sign assessments should be such that it allows the blood draw (eg, PK blood sample) to occur at the time points indicated in Appendix C Table 3 Schedule of assessment for olaparib + ceralasertib (AZD6738) combination therapy

.

6.2 Treatment period

All procedures to be conducted during the treatment period will be performed according to the assessment schedule (see Appendix C Table 3 Schedule of assessment for olaparib + ceralasertib (AZD6738) combination therapy

).

Whenever vital signs and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: vital signs and then blood draws. The timing of the vital signs assessments should be such that it allows the blood draw (eg, PK blood sample) to occur at the time points indicated in Appendix C Table 3 Schedule of assessment for olaparib + ceralasertib (AZD6738) combination therapy

.

6.3 Follow-up period

All procedures to be conducted during the follow-up period will be performed according to the assessment schedule (see Appendix C Table 3 Schedule of assessment for olaparib + ceralasertib (AZD6738) combination therapy

).

A discontinuation assessment will be performed at the time investigational product is permanently discontinued. In addition patients should be followed up for 30 days after the last dose of study treatment for any new reports of adverse events and other study assessments. Patients should also be asked about concomitant medications at this follow-up. Patients will continue to be followed until disease progression.

7. STUDY ASSESSMENTS

Please also refer to Section 6 of the master protocol for the study assessments applicable to all arms in the study. Additional study assessments applicable to Arm C are listed below.

Prior to discharge from each in-patient and clinic visit, the Investigator or their deputy will be responsible for reviewing all available safety data, including vital signs and ECGs.

7.1.1 Physical examination

A complete physical examination with weight will be performed at the visits as indicated in the study plan and clinically indicated. Height will be recorded at screening only. The following will be assessed: general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, abdomen, musculo-skeletal (including spine and extremeities) and neurological systems. Clinically relevant worsening of physical examination findings will be recorded as AEs.

Performance status will be assessed at the visits as indicated in the study plan according to US ECOG criteria (see Section 6.3.1 of master protocol for ECOG assessment parameters).

7.1.2 Vital signs

Any changes in vital signs should be recorded as an AE if applicable.

7.1.2.1 Supine blood pressure and pulse rate

Blood pressure and pulse rate will be assessed according to the study plan and as clinically indicated at any other time.

Blood pressure and pulse rate will be measured preferable using a semi-automated BP recording device with an appropriate cuff size after 10 minutes rest.

7.1.2.2 Body temperature

Body temperature will be measured in degrees Celsius at the visits indicated in the study plan.

7.1.3 ECG

Triplicate ECG recordings are required within 7 days prior to starting study treatment (i.e, during screening), as well as at the times as shown in the study plan.

Triplicate ECG recordings should be taken within an approximate 5-minute period. Additional ECGs may be taken at any other time the Investigator deems necessary for safety during the administration period. The patients will rest for at least 10 minutes before the start of each recording and they must be in the same supine body position (maximum 30 degrees flexion in the hip and feet not in contact with the footboard) at the recording time point. The Investigator or designated physician will review the paper copies of each of the timed 12-lead ECGs on each of the study days when they are collected and assess whether they are clinically significantly abnormal/ not clinically significantly abnormal. If there is a clinically significant abnormal finding, the Investigator will record it as an AE on the eCRF. For information on recording of AEs see Section 7.3. The original ECG traces must be stored in the patient medical record as source data.

A standardised ECG machine should be used and the patient should be examined using the same machine throughout the study, where feasible. ECGs will be recorded at 25 mm/sec. Attention should be paid to any detected increases in QTc interval. Patients who develop asingle resting value of QTc interval of >450 msec/male and >470 msec/female or a shift frombaseline of 60ms should stop taking the study treatment. Dosing can be resumed at a reduced dose after return of the resting QTc interval to pre-treatment status has been confirmed and correction of possible electrolyte imbalance has been made. Monitoring of QTc, checking and correction of abnormal electrolyte levels and renal function are advised, especially in case of severe/prolonged diarrhoea. If QTc increases markedly from baseline, but stays below the above limits, a cardiologist's advice should be sought and Sponsor should be contacted for advice and notification. The concomitant use of ondansetron (known to prolong the QTc interval in rare cases, per labelling) should be taken into account when interpreting QTc changes.

7.1.4 Laboratory safety assessment

Blood and urine samples for safety assessments will be taken at the visits as indicated in the study plan. All laboratory assessments described will be performed at the local laboratories. Additional safety samples may be collected if clinically indicated at the discretion of the Investigator.

Laboratory tests do not need to be repeated at baseline if the baseline visit is within 3 days of the screening sample. The date, time of collection and results of each collection will be recorded in the appropriate CRF.

Laboratory values that meet the criteria for CTCAE grade 3 or have changed significantly from baseline and are considered to be of clinical concern will be repeated/confirmed within 7 days and followed up as appropriate.

The following laboratory variables will be measured:

Appendix C Table 4 Laboratory safety assessment

Clinical chemistry	**Haematology**
Serum (S)-Albumin	Blood (B)-Haemoglobin
	B-Leukocyte
S-ALT	B-Absolute leukocyte differential count*
S/P-AST	Neutrophils
S-Alkaline phosphatase	Lymphocytes
S-Bilirubin, total	Monocytes
S-Calcium	B-Platelet count
S-Creatinine	B-Mean Cell Volume
S-Potassium	**Coagulation****
S-Sodium	B-INR
S-Urea nitrogen or Urea	APTT
S– C-reactive protein	**Urinalysis**
S – total protein	Urine (U)-Protein/ Albumin
Pregnancy tests	U-Glucose
	U-Blood/ Hb / Erythrocytes

* If absolute differentials not available please provide % differentials
** Coagulation tests will be performed at screening and if clinically indicate. Each coagulation result will be recorded on the eCRF. Patients taking warfarin may participate in this study. However, it is recommended that INR be monitored carefully at least once per week for the first month, then monthly if the INR is stable.

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be retained at centre as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported, see Section 7.3.7 in the master protocol.

NB. In case a subject shows an AST or ALT ≥ 3xULN or total bilirubin ≥ 2xULN please refer to Appendix E ‘Actions required in cases of combined increase of aminotransferase and total bilirubin – Hy’s Law’ for further instructions.

Blood volumes can be found in the Laboratory Manual.

7.1.5 Bone marrow or blood cytogenetic samples

Bone marrow or blood cytogenetic samples may be collected for patients with prolonged haematological toxicities as defined in Section Management of prolonged haematological toxicities while on study treatment..

Bone marrow analysis should include an aspirate for cellular morphology, cytogenetic analysis and flow cytometry, and a core biopsy for bone marrow cellularity. If it is not possible to conduct cytogenetic analysis or flow cytometry on the bone marrow aspirate, then attempts should be made to carry out the tests on a blood sample. Full reports must be provided by the investigator for documentation on the Patient Safety database. These data are not required to be entered into eCRF.

7.2 Pharmacokinetics

7.2.1 Collection of pharmacokinetic samples

The following PK sampling will be performed on Cycle 1.

- Day 1; sampling times - 1-3 hours, 3-6 hours and 6-12 hours post-treatment
- Day 7; sampling times - pre-dose and 0.5-1 hour, 1-3 hours, 3-6 hours and 6-12 hours post-treatment.

The following PK samples will be performed on Day 1 of Cycles 2 to 6 only.

- Cycle X, Day 1: Single sample 1-6 hours post treatment

Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual. The date and time of collection of each sample will be recorded in the medical notes and eCRF. All the post-dose samples collected within 10% of the scheduled time (e.g. ± 6 minutes for 60 minute sample) will be considered protocol compliant.

PK samples are to be taken as blood sample (4 mL) for determination of olaparib and ceralasertib concentrations in plasma. It is essential that PK blood sampling is conducted at the planned study timepoints. Patients should be instructed to fast and hold their morning dose of ceralasertib/olaparib on any day PK sampling is scheduled so it may have timed administration in the clinic. Any residual sample remaining after PK analysis has been performed may be used for exploratory biomarker research and characterisation of metabolites, if consent for this exploratory research has been obtained.

7.2.2 Determination of drug concentration in pharmacokinetic samples

Samples for determination of drug concentration will be analysed by Third party bioanalytical laboratory on behalf of AstraZeneca Full details of the analytical methods used will be described in a separate bioanalytical report.

Pharmacokinetic samples will be disposed of after the Bioanalytical Report finalization or six months after issuance of the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses. Pharmacokinetic samples may be disposed of or destroyed and anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the CSR but separately in a Bioanalytical Report. Any residual back-up PK samples may be used for future exploratory biomarker research (in this case, residual back-up PK samples will be shipped to the AZ biobank; see details in the Laboratory Manual).

7.3 Efficacy Analysis

See Section 6.1 of the master protocol.

Efficacy in Arm C will be assessed using RECIST 1.1 criteria on images collected at baseline and then at 8 weeks, then at 12 weeks and then every 8 weeks (all ± 1 week) for the first 72 weeks and then every 12 weeks (± 1 week) thereafter, relative to the first day of investigational drug administration, up to objective disease progression by RECIST 1.1. After that, patients will then be followed for survival, regardless of whether study treatment is discontinued or delayed and/or protocol violations, unless they withdraw consent.

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

7.4 Biomarker analysis

Biological samples (eg, archival tumour samples, tissue and/or blood) will be collected as detailed in the Laboratory Manual in order to carry out retrospective biomarker analysis to assess correlations with disease activity, effects of study drug, clinical outcomes and toxicity.

7.4.1 CCI [redacted]

CCI [redacted] Such analysis may include, but is not restricted to:

- CCI [redacted]

- CCI [redacted]

Details of sample processing methods can be found in the study Laboratory Manual.

Results of these other exploratory analyses will not be reported in the CSR, but may be added in an appendix to the CSR. No formal statistical analysis is planned.

7.4.2 Collection of peripheral blood for pharmacodynamic biomarker analysis

Peripheral blood samples will be collected and analyzed for downstream analysis of ATR pathway biomarkers that may include but are not limited to: CCI [redacted] in purified peripheral blood mononuclear cells (PBMC) samples, possibly including CCI [redacted]. Circulating soluble factors such as cytokines that may include but are not limited to GM-CSF, M-CSF and IFNγ may be assessed. Additional details of blood collection, shipping and storage of samples for biomarker assays can be found in the laboratory manual.

Peripheral blood samples will be collected for pharmacodynamic biomarker analysis at predose on Cycle 1 Day 1, 6 hours post dose on Cycle 1 Day 7, Cycle 1 Day 15, Day 1 of each subsequent cycle and at End of Treatment. Details for processing, handling, and shipping are provided in the Laboratory Manual.

In addition, blood samples will be collected in Streck DNA BCT tubes, and processed to isolate CCI [redacted]. Additional samples may also be taken to generate circulating mRNA for storage and subsequent analyses. These samples will be used to assess the expression of genes and/or the presence of mutations in key driver genes and their association with response or resistance.

The timing of the pharmacodynamic biomarker samples may be adjusted during the study, dependent on emerging data, in order to ensure appropriate characterisation of biomarkers.

7.4.3 Collection of archival tumour samples

Formalin fixed tumour tissue embedded in paraffin blocks are optional for all dosed patients. If baseline biopsy samples can also be collected, retrieval of the archival diagnostic tumour material is still highly encouraged, to provide data on how the tumour has evolved since

diagnosis. Archival samples from either primary or metastatic tumour will be accepted but tissue from the primary tumour is preferred. Tissue from the most recent biopsy would be preferred where a patient has archival tissue samples from multiple time points.

Freshly prepared unstained slides (minimum 10, preferably 20), 4 micron sections from the archival tumour block are accepted if tumour blocks cannot be submitted, however tumour tissue blocks are preferred. Blocks will be repatriated to clinical sites upon request.

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

7.4.4 Collection of fresh biopsy samples

Collection of serial tumour biopsies will be encouraged during the study. For patients with accessible tumours where patients' consent has been obtained, a fresh tumour biopsy prior to first dose, following ceralasertib and olaparib treatment (on Cycle 1 Day 7), and following progression will be analyzed for downstream effects on ATR pathway that may include but are not limited to biomarkers [redacted], [redacted], [redacted] On-treatment biopsy timing may be refined with emerging pharmacokinetic and/or pharmacodynamic data during the course of the trial. Accessible lesions are defined as tumour lesions which are amenable to repeat biopsy, unless clinically contraindicated or the patient has withdrawn consent. Failure to obtain sufficient tumour sample after making best efforts to biopsy the tumour will not be considered a protocol deviation.

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

7.4.5 [redacted]

[redacted]

Details on processes for collection and shipment and destruction of these samples can be found in [redacted] or in the Laboratory Manual.

7.5 Biological sampling procedures

7.5.1 Volume of blood

The total volume of blood that will be drawn from each patient in this study during screening, treatment and follow-up is shown in the Laboratory Manual.

7.5.2 Handling, storage and destruction of biological samples

The samples will be used up, or disposed of after analyses or retained for further use as described below.

Any pharmacokinetic sample remaining after analysis for ceralasertib and its metabolites may be used for biomarker analyses. These analyses are for AstraZeneca use only and will not be included in the Clinical Study Report.

Biological samples for future research will be retained at Sponsor or its designee for a maximum of 15 years following the finalisation of the Clinical Study Report. The results from future analysis will not be reported in the Clinical Study Report but separately in a Clinical Study Report Addendum, Scientific Report or Scientific Publication.

7.5.2.1 Pharmacokinetic samples

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples and reported in a separate bioanalytical report.

The results from the investigation will not be reported in the Clinical Study Report but separately in a bioanalytical report.

7.5.2.2 Samples for exploratory research

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

Each sample for exploratory research will be identified with the study number and patient enrolment number. In this way exploratory biomarker and genetic data may be correlated with clinical data, samples destroyed in the case of withdrawal of consent and regulatory audit enabled.

Where genetic analysis will be undertaken, no personal details identifying the individual will be available to any person (AstraZeneca employee or contract laboratory staff) working with the DNA.

7.5.3 Labelling and shipment of biohazard samples

The Principal Investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix D of this Clinical Study Protocol ‘IATA 6.2 Guidance Document’.

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

All archival tumour samples should be shipped at ambient temperature as per the Laboratory Manual to the AstraZeneca designated central Contract Research Organisation. Please refer to section 6.6.5 of the master protocol for details about chain of custody of biological samples.

7.5.4 Withdrawal of informed consent for donated biological samples

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

As collection of these biological samples is a voluntary part of the study then the patient may continue in the study.

The Principal Investigator:

- Ensures AstraZeneca is notified immediately of the patient's withdrawal of informed consent to the use of donated biological samples
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of/destroyed, and the action documented
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the signed document returned to the study site
- Ensures that the patient and AstraZeneca are informed about the sample disposal

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

8. SAFETY REPORTING AND MEDICAL MANAGEMENT

Please refer to Section 7 of the master protocol for details of reporting AEs, SAEs, AEs of special interest, paternal exposure, and management of investigational product (IP) related toxicities applicable to all arms in the study. Additional details for reporting AE, SAEs, AEs of special interest, paternal exposure, and management of IP related toxicities applicable to Arm C are described below.

8.1 Reporting of adverse events

8.1.1 Time period for collection of adverse events

AEs and SAEs will be recorded from the time of informed consent, throughout the treatment period, and including the follow-up period (the follow-up period is 30 days after the last dose of study treatment of ceralasertib and olaparib). SAEs occurring in the follow-up period should be reported in the usual manner.

8.1.2 Follow-up of unresolved adverse events

Please refer to Section 7.3.2 of the master protocol for details of follow-up of unresolved adverse events.

8.1.3 Reporting of serious adverse events

Please refer to Section 7.4 of the master protocol for details of reporting of serious adverse events.

8.1.4 Post study events

After the patient has been permanently withdrawn from the study, there is no obligation for the Investigator to actively report information on new AEs or SAEs occurring in former study patients after the arm designated number of days, or 30 day safety follow-up period. However, if an Investigator learns of any SAEs, including death, at any time after the patient has been permanently withdrawn from the study, and he/she considers there is a reasonable possibility that the event is related to the study treatment, the Investigator should notify AstraZeneca, Patient Safety, or its representative.

8.2 Pregnancy

8.2.1 Maternal exposure

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

If any pregnancy occurs in the course of the study, the Investigator or other study center personnel must inform the appropriate AstraZeneca representatives within 1 calendar day (ie, immediately but no later than 24 hours of when he or she becomes aware of it).

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs, and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

8.2.2 Paternal exposure

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

8.3 Overdose of either olaparib or ceralasertib

There is no specific treatment in the event of olaparib or ceralasertib overdose, and no symptoms of overdose are established. In the event of overdose, physicians should follow general supportive measures and should treat symptomatically.

8.4 Dose modifications and management of investigational product related toxicities

Guidelines for the management of hematological and non-hematological AEs for ceralasertib and olaparib are described below. Given the aggressive nature of relapsed or refractory SCLC and the lack of an effective standard of care in this clinical setting, doses of ceralasertib and olaparib will be modified by cycle (see Section 2.1 of the CSP). Subsequent cycles will be further adjusted to patient tolerance and investigator judgement.

Toxicity will be assessed utilizing the NCI Common Terminology Criteria for Adverse Event (CTCAE) version 4.03 unless otherwise specified. Every effort should be made to administer trial treatment at the planned dose and schedule. However, patients experiencing toxicities related to the trial treatment may have their dose modified as outlined in this section.

Any toxicity observed during the course of the study could be managed by interruption of study treatment or dose reductions, and intiation of supportive care as deemed appropriate by the investigator. In the event that a patient has not recovered sufficiently to enable the next chemotherapy cycle to start, then the cycle should be delayed until the toxicity has recovered sufficiently to allow further dosage. The maximum cycle delay is permitted in 28 days. Repeat dose interruptions are allowed as required, for a maximum of 28 days on each occasion. Any patient requiring a toxicity related dose delay of more than 28 days from the intended day of the next scheduled dose must be discontinued from the study unless there is approval from the Study Physician for the patient to continue.

If Day 1 treatment with either ceralasertib or olaparib is interrupted, then both study medications will be delayed until the combination can be resumed. Dose adjustments will be based on the organ system exhibiting the greatest degree of toxicity.

8.4.1 Dose Reduction: Ceralasertib + Olaparib Combination

For ceralasertib, study treatment can be dose reduced according to the following dose modification table. A maximum of 2 dose reduction steps are permitted. If after the second dose reduction treatment is not tolerated, no further dose reduction is allowed, and study treatment should be discontinued. Dose re-escalation is not permitted. Further dose modifications are described in Appendix C Table 5 below.

Appendix C Table 5 : Cohort C Guidance for dose reductions for ceralasertib and olaparib*

Dose Level	Ceralasertib	Olaparib
Initial dose level	160 mg QD Days 1-7	300 mg BID Days 1-28
1st dose reduction	Dose reduce either AZD6738 or Olaparib or Both	
Haematological Toxicity	160mg QD Days 1-4	250 mg BID Days 1-28
Non-Haematological Toxicity	120mg QD Days 1-7	250 mg BID Days 1-28
2nd dose reduction	Dose reduce either Ceralasertib or Olaparib or Both	
	120 mg QDQ Days 1-4	200 mg BID Days 1-28
3rd dose reduction: No further reduction permitted, withdraw patient and treat as clinically indicated. Dose must not be re-escalated even if toxicities have resolved in subsequent cycles.		

* Ceralasertib and olaparib may be reduced stepwise within each dose reduction level e.g., dose reduce olaparib first followed by ceralasertib if the AE recurs. Dose reductions for anaemia should occur for olaparib first (with consideration to a simultaneous dose reduction in ceralasertib depending on the severity, duration and recurrence of the anaemia). If a dose reduction is required for neutropenia, leukopenia and thrombocytopenia, olaparib and ceralasertib should be dose reduced simultaneously as there is a greater frequency associated with ceralasertib. For a second dose-reduction, follow the guidance above on which of either, or both agents, to dose-reduce depending on the observed toxicity.

Appendix C Table 8 provides guidance for hematologic toxicity (neutropenia, leukopenia and thrombocytopenia) observed any time during the study treatment period. **For Day 1 of each cycle please check the required blood counts to commence treatment in Appendix C Table 6.**

8.4.2 Management of Haematological Toxicities for Ceralasertib and Olaparib Combination

Complete blood counts will be obtained for all patients at the beginning of each treatment cycle (Day 1) and should be checked by the Investigator prior to dosing the patient. If haematologic toxicity occurs treatment should be modified as below (Appendix C Table 6), and ANC and platelets should be monitored weekly (more often as clinically indicated until recovery). If haematologic parameters do not recover within 28 days, the patient should be removed from the study treatment.

Appendix C Table 6: Day 1 Haematologic dose modifications and management for ceralasertib plus olaparib combination

Treatment day blood counts and toxicity			
ANC		**Platelets**	**Action**
≥1500/μL	And	≥100,000/μL	No dose modification or interruption
<1500/μL	Or	<100,000/μL	Delay by 1week intervals until recovery

8.4.2.1 Management of Anemia

Common treatable causes of anaemia (e.g., iron, vitamin B12 or folate deficiencies and hypothyroidism) should be investigated and appropriately managed. In some cases management of anaemia may require blood transfusions. For cases where patients develop prolonged haematological toxicity (≥2 week interruption/delay in study treatment due to CTC grade 3 or worse anaemia and/or development of blood transfusion dependence), refer to section below on **Section 8.4.2.3** 'Management of prolonged haematological toxicities while on study treatment'.

Appendix C Table 7: Management of anemia for ceralasertib plus olaparib combination

Haemoglobin	**Action to be taken**
Hb <10 ***but*** **≥8 g/dL (CTCAE Grade 2)**	Give appropriate supportive treatment and investigate causality. Investigator judgement to continue study treatment with supportive treatment (eg transfusion) *or* interrupt dose for a maximum of 4 weeks. If repeat Hb**<10** ***but*** **≥8 g/dL**, dose interrupt (for max of 4 weeks) until Hb ≥10 g/dL and upon recovery dose reduction to **250 mg BID** as a first step and to **200 mg BID** as a second step may be considered.

Haemoglobin	Action to be taken
Hb <8 g/dL (CTCAE Grade 3)	Give appropriate supportive treatment (eg, transfusion) and investigate causality. Interrupt study treatment for a maximum of 4 weeks until improved to Hb ≥10 g/dL. Upon recovery dose reduce to **250 mg BID** as a first step and to **200 mg BID** as a second step in the case of repeat Hb decrease.

Transfusion therapy may be required to maintain Hb levels >80g/L throughout the first three months of therapy to avoid dose reduction or interruption of olaparib. If a patient requires transfusions on a regular basis in the first 3 months, or cannot tolerate or be supported by transfusions, the dose of olaparib can be reduced.

8.4.2.2 Management of neutropenia, leukopenia and thrombocytopenia for ceralasertib plus olaparib combination

In the event of neutropenia, leukopenia or thrombocytopenia, ceralasertib and olaparib dosing should be halted until ANC and platelet count are restored to within the acceptable criteria:

- ANC 1.5×10^9 /L
- Platelets 100×10^9 /L

AEs of neutropenia and leukopenia should be managed as deemed appropriate by the Investigator with close follow up and interruption of study drug if CTC Grade 3 or worse neutropenia occurs.

Granulocyte colony-stimulating factor (G-CSF) should be used according to local prescribing guidance. Primary prophylaxis with G-CSF is not recommended, however, if a patient develops febrile neutropenia, study treatment should be stopped and appropriate management including G-CSF should be given according to local hospital guidelines. Please note that G-CSF should not be used within at least 24 hours (7 days for pegylated G-CSF) of the last dose of study treatment, unless absolutely necessary. Platelet transfusions, if indicated should be done according to local hospital guidelines. List all interventions of these types into the appropriate CRF pages.

Appendix C Table 8: Management of neutropenia, leukopenia and and thrombocytopenia

Toxicity	Study treatment dose adjustment
CTCAE Grade 1-2	Investigator judgement to continue treatment or if dose interruption, this should be for a maximum of 4 weeks; appropriate supportive treatment and causality investigation
CTCAE Grade 3-4	Dose interruption until recovered to CTCAE grade 1 or better for a maximum of 4 weeks. If repeat CTCAE grade 3-4 occurrence, dose reduce olaparib to 250 mg BID as a first step and 200 mg BID as a second step

8.4.2.3 Management of prolonged haematological toxicities while on study treatment.

If a patient develops prolonged haematological toxicity such as:

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

Check weekly differential blood counts including reticulocytes and peripheral blood smear. If any blood parameters remain clinically abnormal after 4 weeks of dose interruption, the patient should be referred to haematologist for further investigations. Bone marrow analysis and/or blood cytogenetic analysis should be considered at this stage according to standard haematological practice. Study treatment should be discontinued if blood counts do not recover to CTC Grade 1 or better within 4 weeks of dose interruption.

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

Further details are provided in the Investigators Brochure.

8.4.2.4 Management of non-haematological toxicity for ceralasertib and olaparib

Acute toxicities in the all treatment arms should be managed as medically indicated, with temporary suspension of IP and initiation of supportive care as clinically indicated by the treating physician. Treatment must be interrupted if any NCI-CTCAE Grade 3 or 4 non hematologic AE occurs which the Investigator considers to be related to the administration of the study treatment(s). Treatment should not be restarted until the toxicity has resolved to Grade ≤1.

Repeat dose interruptions are permitted, for a maximum of 28 days. Any patient who develops a Grade 3 or 4 non-haematologic toxicity that does not resolve to ≤ Grade 1 within this period, should be removed from the study treatment. Once a dose is reduced, re escalation is not permitted.

A summary of the dose reduction guidance for ceralasertib and olaparib is presented earlier.

At the first occurrence of CTCAE grade 3 and 4 non-haematological toxicity, ceralasertib and olaparib should be held until resolution of toxicity. At the resolution of the first occurrence of any of these toxicities, no change must be made to dose. At the second occurrence, upon resolution of toxicity, ceralasertib and/or olaparib should be reduced by the 1st dose reduction for non-haematological toxicity to 120 mg qd for 7 days and/or olaparib 250 mg BID q 12 hours daily (Appendix C Table 5 and Appendix C Table 9) Despite this change, at the third occurrence, upon resolution of toxicity, ceralasertib and/or olaparib should be reduced by the 2nd dose reduction to 120 mg qd for 4 days and 200 mg bid q 12 hours daily (Appendix C Table 5 and Appendix C Table 9). If despite these changes, there is a fourth occurrence of toxicity, the patient should permanently discontinue study drug. Please note that, for each dose reduction, the investigator may choose to reduce ceralasertib or olaparib or both drugs. If only one drug is dose reduced, the second drug may be reduced as an additional step. Refer to Appendix C Table 9 for specific dose modification guidance regarding non-haematological toxicity.

Appendix C Table 9: Summary of guidance on the management of non-haematologic toxicity for ceralasertib and olaparib

Toxicity	Ceralasertib and olaparib
Any non-haematologic toxicity (CTCAE grade ≥ 3)	1st occurrence Withhold dose and monitor at least weekly for up to 28 days until recovery to ≤CTCAE grade 1 then resume at original dose level. If a clinical CTCAE give supportive measures and rule out other causes; if a laboratory AE is not resolving within two weeks contact Sponsor for guidance If symptoms do not recover to ≤CTCAE grade 1, contact Sponsor and consider discontinue ceralasertib and olaparib . 2nd occurrence Withhold dose for up to 28 days until recovery to ≤CTCAE grade 1 then resume at 1st reduced dose level for non-haematological toxicity (see Appendix C, table 4). The investigator may choose to reduce ceralasertib or olaparib or both drugs. If only one drug is dose reduced, the second drug may be reduced as an additional step if the toxicity recurs. If symptoms do not recover to ≤CTCAE grade 1, contact Sponsor and consider discontinue ceralasertib and olaparib. 3rd occurrence Withhold dose for up to 28 days until recovery to ≤CTCAE grade 1 then resume at 2nd reduced dose level for non-haematological toxicity (see **Appendix C, table 4**). The investigator may choose to reduce ceralasertib or olaparib or both drugs. If only one drug is dose reduced, the second drug may be reduced as an additional step if the toxicity recurs. If symptoms do not recover to ≤CTCAE grade 1, contact Sponsor and consider discontinue ceralasertib and olaparib.

Toxicity	Ceralasertib and olaparib
	4th occurrence Off-study drug

8.4.2.5 Management of new or worsening pulmonary symptoms

If new or worsening pulmonary symptoms (eg, dyspnoea) or radiological abnormality occurs, an interruption in study treatment dosing is recommended and a diagnostic workup (including a high resolution CT scan) should be performed, to exclude pneumonitis. Following investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, then study treatment can be restarted, if deemed appropriate by the investigator. If significant pulmonary abnormalities are identified, these need to be discussed with the AstraZeneca Study Physician.

8.4.2.6 Renal Impairment

If subsequent to study entry and while still on study therapy, a patient's estimated CrCl falls below the threshold for study inclusion (≥51 ml/min), retesting should be performed promptly. A dose reduction is recommended for patients who develop moderate renal impairment (calculated creatinine clearance by Cockcroft-Gault equation of between 31 and 50 ml/min) for any reason during the course of the study: the dose of olaparib should be reduced to 200mg BID. Because the CrCl determination is only an estimate of renal function, in instances where the CrCl falls to between 31 and 50 mL/min, the investigator should use his or her discretion in determining whether a dose change or discontinuation of therapy is warranted or a more formal test of creatinine clearance determination should be performed.

Olaparib has not been studied in patients with severe renal impairment (creatinine clearance ≤ 30 ml/min) or end-stage renal disease; if patients develop severe impairment or end stage disease is it recommended that olaparib be discontinued.

8.4.2.7 Management of nausea and vomiting

Events of nausea and vomiting are known to be associated with olaparib treatment. They are generally mild to moderate (CTCAE grade 1 or 2) severity, intermittent and manageable on continued treatment. The first onset generally occurs in the first month of treatment with the incidence of nausea and vomiting not showing an increase over the treatment cycles.

No routine prophylactic anti-emetic treatment is required at the start of study treatment, however, patients should receive appropriate anti-emetic treatment at the first onset of nausea or vomiting and as required thereafter, in accordance with local treatment practice guidelines.

8.4.2.8 Interruptions for intercurrent non-toxicity related events

Study treatment dose interruption for conditions other than toxicity resolution should be kept as short as possible. If a patient cannot restart study treatment within 4 weeks for resolution of intercurrent conditions not related to disease progression or toxicity, the case should be discussed with AZ study physician.

All dose reductions and interruptions (including any missed doses), and the reasons for the reductions/interruptions are to be recorded in the eCRF.

Study treatment should be stopped at least 3 days prior to planned surgery. After surgery study treatment can be restarted when the wound has healed. No stoppage of study treatment is required for any biopsy procedure.

Study treatment should be discontinued for a minimum of 3 days before a patient undergoes radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.

Because the AEs related to olaparib may include asthenia, fatigue and dizziness, patients should be advised to use caution while driving or using machinery if these symptoms occur.

9. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

9.1 Identity of investigational product(s)

Investigational product	Dosage form and strength
Ceralasertib	20 mg or 100 mg tablets
Olaparib	100 mg or 150 mg film-coated tablets

9.1.1 Ceralasertib

AstraZeneca will supply ceralasertib tablets for oral use. The tablets will be supplied at 2 strengths (20 mg and 100 mg) in high-density polyethylene bottles, which sufficiently protects the drug from light. Ceralasertib coated tablets contain a blend of ceralasertib, mannitol, microcrystalline cellulose, sodium starch glycolate, magnesium stearate and silicon dioxide. The coating is Opadry® II white.

The different tablet strengths should not be combined in the same bottle at any time. Additional information about the IP may be found in the IB.

Ceralasertib is taken PO daily on Days 1 to 7 of each treatment cycle at about the same time each day. Treatment cycles are every 28 days. Ceralasertib should be taken with approximately 8 ounces of water. When ceralasertib is administered in combination with olaparib, patients must fast as directed for at least 2 hours prior to the dosing and for at least 1

hour after the dose. When olaparib is given on its own, the olaparib tablet formulation can be given without regard to food.

If a patient misses a daily dose, a double dose should not be taken on the next day. If vomiting occurs after a patient takes the ceralasertib dose, the patient should not take the dose again unless they can count all of the taken tablets.

9.1.2 Olaparib

Olaparib is presented for oral administration as a green, film-coated tablet containing 25 mg, 100 mg, 150 mg or 200 mg of drug substance. The 100 mg strength is also available as a yellow, film-coated tablet.

Olaparib tablets are supplied in high-density polyethylene (HDPE) bottles containing desiccant. Bottles are secured with a child-resistant closure; induction-sealed membranes provide tamper evidence.

The 25 mg, 100 mg, 150 mg and 200 mg strengths of olaparib tablets are composed of the same constituents. The tablet cores comprise: olaparib, copovidone, colloidal silicon dioxide, mannitol and sodium stearyl fumarate. The composition of the green tablet film coating is: hydroxypropyl methylcellulose (hypromellose), macrogol 400 (polyethylene glycol 400), titanium dioxide, iron oxide yellow and iron oxide black. The yellow tablet film coating only differs from the green film coating with the omission of iron oxide black.

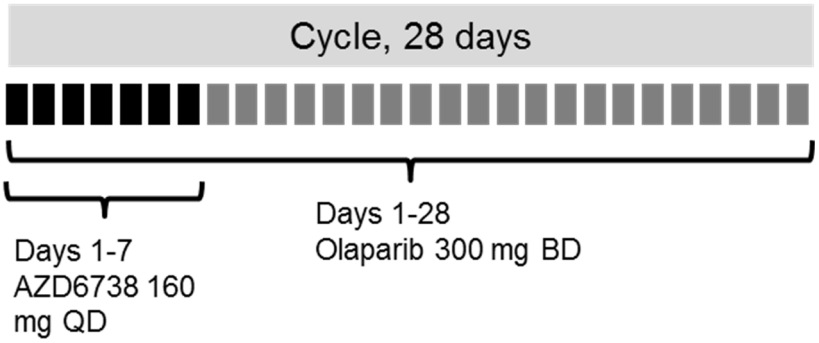
Olaparib tablets are taken PO, twice daily, approximately 12 hours apart. When ceralasertib is administered in combination with olaparib, patients must fast as directed for at least 2 hours prior to the dosing and for at least 1 hour after the dose. When olaparib is given on its own, the olaparib tablet formulation can be given without regard to food.

9.2 Dose and treatment regimens

For Arm C, up to 20 patients will be enrolled, and all patients will receive:

Ceralasertib 160 mg QD PO for 7 days from Day 1 + olaparib 300 mg BID PO from Day 1 for 28 days; q4w until PD.

Appendix C Figure 3 Ceralasertib + olaparib therapy dosing schedule



9.3 Labeling

Please refer to Section 8.3 of the master protocol for details regarding labelling applicable to all arms.

9.4 Storage

Please see Section 8.4 of the master protocol.

9.5 Compliance

Dosing compliance will be reviewed with the patient at the beginning of each new treatment cycle when ceralasertib and olaparib is dispensed. All patients will be required to complete a dosing diary, which must be returned to the clinic for review at each visit. The patient should be instructed to record each date and time the dose(s) was taken in the dosing diary. If a dose is missed, the reason must be noted in the diary. A copy of the dosing diary is provided in the study reference materials.

Patients should be advised to return any unused ceralasertib and olaparib in the original bottles, in addition to returning any empty bottles.

The administration of all study drugs (including IPs) should be recorded in the appropriate sections of the case report form (CRF).

9.6 Accountability

Please see Section 8.6 of the master protocol.

9.7 Concomitant and other treatments

Please refer to Section 8.7 of the master protocol for details regarding concomitant and other treatments applicable to all arms. Details regarding concomitant and other treatments applicable to Arm C are described below.

Patients must comply with the concomitant treatment information described in the core study protocol and those described in the olaparib and ceralasertib Investigators' Brochure.

9.7.1 Medications that may NOT be administered

- No other anti-cancer therapy (chemotherapy, immunotherapy, hormonal therapy (Hormone replacement therapy (HRT) and stable treatment of > 6 months with LHRH analogues are acceptable), radiotherapy (palliative radiotherapy is permitted, if study treatment has been withheld for at least 3 days, see Section 9.7.5), biological therapy or other novel agent) is to be permitted while the patient is receiving study medication.

- Live virus and bacterial vaccines should not be administered whilst the patient is receiving study medication and during the 28 day follow up period. An increased risk of infection by the administration of live virus and bacterial vaccines has been observed with conventional chemotherapy drugs and the effects with study medication are unknown.

- Strong or Moderate CYP3A inhibitors (See Appendix I Disallowed Medications and Medications to be Administered with Caution

- Known strong CYP3A inhibitors (e.g., itraconazole, telithromycin, clarithromycin, boosted protease inhibitors, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil) should not be taken with study treatment.

- If there is no suitable alternative concomitant medication then the dose of study treatment should be reduced for the period of concomitant administration. Suggested dose reductions for olaparib are described below. The dose reduction of study treatment should be recorded in the CRF with the reason documented as concomitant CYP3A inhibitor use.

- Strong CYP3A inhibitors - reduce the dose of olaparib to 100mg BID for the duration of concomitant therapy with the strong inhibitor and for 5 half lives afterwards.

- Moderate CYP3A inhibitors - reduce the dose of olaparib to 150mg BID for the duration of concomitant therapy with the moderate inhibitor and for 3 half lives afterwards.After the washout of the inhibitor is complete, the olaparib dose can be re-escalated.

- Strong or Moderate CYP3A inducers (See Appendix D International Airline Transportation Association 6.2 Guidance Document:

- Strong (e.g., phenobarbital, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine, enzalutamide and St John's Wort) and moderate CYP3A inducers (eg. bosentan, efavirenz, modafinil) of CYP3A should not be taken with study treatment. If the use of any strong or moderate CYP3A inducers are considered necessary for the patient's safety and welfare this could diminish the

clinical efficacy of study treatment. If a patient requires use of a strong or moderate CYP3A inducer then they must be monitored carefully for any change in efficacy of study treatment.

- P-gp inhibitors (See Appendix I Disallowed Medications and Medications to be Administered with Caution):

- It is possible that co-administration of P-gp inhibitors (eg amiodarone, azithromycin) may increase exposure to study treatment. Caution should therefore be observed.

9.7.2 Effect of olaparib on other drugs

- Based on limited in vitro data, olaparib may increase the exposure to substrates of CYP3A4, , OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K.

- Based on limited in vitro data, olaparib may reduce the exposure to substrates of CYP2B6.

- Caution should therefore be observed if substrates of these isoenzymes or transporter proteins are co-administered.

Examples of substrates include:

- CYP3A4 – simvastatin, cisapride, cyclosporine, ergotalkaloids, fentanyl, pimozide, sirolimus, tacrolimus and quetiapine

- CYP2B6 – bupropion, efavirenz

- OATP1B1 - bosentan, glibenclamide, repaglinide, statins and valsartan

- OCT1, MATE1, MATE2K – metformin

- OCT2 - serum creatinine

- OAT3 -furosemide, methotrexate

After commencement of IP if the use of any potent inducers or inhibitors of CYP3A4/5 are considered necessary for the patient's safety and welfare, the investigator must contact the AstraZeneca Study Physician. A decision to allow the patient to continue study treatment will be made on a case-by-case basis.

9.7.3 Anticoagulant Therapy

Patients who are taking warfarin may participate in this trial; however, it is recommended that prothrombin time (international normalised ratio (INR) and activated partial thromboplastin time (APTT)) be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Subcutaneous heparin is permitted.

9.7.4 Anti-emetics/Anti-diarrhoeals

From the time the subject commences study medication, should the patient develop nausea, vomiting and / or diarrhoea, then these symptoms should be reported as AEs and appropriate treatment for the event given. All treatments should be recorded.

9.7.5 Palliative radiotherapy

Palliative radiotherapy may be used for the treatment of pain at the site of bony metastases that were present at baseline. Study treatment should be discontinued for a minimum of 3 days before a patient undergoes therapeutic palliative radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered, provided the investigator does not feel that these pains are indicative of clinical disease progression during the study period.

9.7.6 Administration of other anti-cancer agents

Patients must not receive any other concurrent anti-cancer therapy, including investigational agents, while on study treatment. Patients may continue the use of bisphosphonates or denosumab for bone disease and corticosteroids for the symptomatic control of brain metastases provided the dose is stable before and during the study and they were started at least 4 weeks prior to beginning study treatment.

9.7.7 Subsequent therapies for cancer

Details of first and subsequent therapies for cancer and/or details of surgery for the treatment of the cancer, after discontinuation of treatment, will be collected. Reasons for starting subsequent anti-cancer therapies including access to other PARP and ATR inhibitors or investigational drugs will be collected and included in the exploratory assessments of OS.

9.7.8 Other concomitant treatment

Other medication other than that described above, which is considered necessary for the patient's safety and well-being, may be given at the discretion of the Investigator and recorded in the appropriate sections of the CRF.

10. STATISTICAL ANALYSES BY ASTRAZENECA

Please refer to Section 9.1 of the master protocol for details regarding statistical analyses applicable to all arms. Additional details regarding statistical analyses applicable to Arm C are described below.

10.1 Adverse events

AEs observed up to 30 days following discontinuation of study treatment or until the initiation of the first subsequent therapy following discontinuation of treatment (whichever occurs first) will be used for the reporting of AE summary tables. This will more accurately depict AEs attributable to study treatment only, as a number of AEs up to 30 days following discontinuation of the study treatment are likely to be attributable to subsequent therapy.

10.2 Study and data management by AstraZeneca

Please refer to Section 10.4 of the master protocol for details of study and data management.

11. ETHICAL AND REGULATORY REQUIREMENTS

Please refer to Section 11.3 of the master protocol for details of ethical and regulatory requirements.

APPENDIX D INTERNATIONAL AIRLINE TRANSPORTATION ASSOCIATION 6.2 GUIDANCE DOCUMENT

Labeling and shipment of biohazard samples

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories. For transport purposes, the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B, or Exempt. There is no direct relationship between risk groups and Categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life threatening, or a fatal disease in otherwise healthy humans or animals. Category A pathogens are, eg, Ebola and Lassa fever virus.

- are to be packed and shipped in accordance with IATA Instruction 602

Category B Infectious Substances are infectious substances that do not meet the criteria for inclusion in Category A. Category B pathogens are, eg, hepatitis A, B, C, D, and E viruses; and human immunodeficiency virus types 1 and 2. They are assigned the following UN number and proper shipping name:

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

Exempt are all other materials with minimal risk of containing pathogens.

- Clinical trial samples will fall into Category B or Exempt under IATA regulations.
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650-compliant packaging.
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content.
- IATA-compliant courier and packaging materials should be used for packing and transportation, and packing should be done by an IATA-certified person, as applicable.
- Samples routinely transported by road or rail are subject to local regulations, which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging/containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

APPENDIX E ACTIONS REQUIRED IN CASES OF INCREASES IN LIVER BIOCHEMISTRY AND EVALUATION OF HY'S LAW

Introduction

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law (HL). It is not intended to be a comprehensive guide to the management of elevated liver biochemistries. Specific guidance on the managing liver abnormalities can be found in Section 6.2.1 of the protocol.

During the course of the study, the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study, according to the definitions below.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than drug-induced liver injury (DILI) caused by the Investigational Medicinal Product (IMP).

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

Definitions

Potential Hy's Law

Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥3× upper limit of normal (ULN) **together with** total bilirubin (TBL) ≥2× ULN at any point during the study following the start of study medication irrespective of an increase in alkaline phosphatase (ALP).

Hy's Law

AST or ALT ≥3× ULN **together with** TBL ≥2× ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, or another drug.

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

Identification of Potential Hy's Law Cases

In order to identify cases of PHL, it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:

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

If a central laboratory is being used

When a patient meets any of the identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the Investigator (also sent to AstraZeneca representative).

The Investigator will also remain vigilant for any local laboratory reports where the identification criteria are met. Where this is the case, the Investigator will:

- Request a repeat of the test (new blood draw) by the central laboratory
- Complete the appropriate unscheduled laboratory case report form (CRF) arm(s) with the original local laboratory test result

When the identification criteria are met from central or local laboratory results, the Investigator will without delay:

- Determine whether the patient meets PHL criteria (see Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

Follow-up

Potential Hy's Law criteria not met

If the patient does not meet PHL criteria, the Investigator will:

- Perform follow-up on subsequent laboratory results according to the guidance provided in the clinical study protocol

Potential Hy's Law criteria met

If the patient does meet PHL criteria, the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment (see Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment)
- Notify the AstraZeneca representative who will then inform the central Study Team

The Study Physician contacts the Investigator to provide guidance, to discuss and agree on an approach for the study patients' follow-up, and for the continuous review of data. Subsequent to this contact, the Investigator will:

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated

- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which tests available in the Hy's Law laboratory kit should be used.

- Complete the three Liver CRF Arms as information becomes available

- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

Review and Assessment of Potential Hy's Law Cases
The instructions in this section should be followed for all cases where PHL criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. The AstraZeneca Medical Science Director and Global Safety Physician will also be involved in this review together with other patient matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF.

- If the alternative explanation is an AE/SAE, record the AE/SAE in the CRF accordingly and follow the AZ standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Report an SAE (report term "Hy's Law") according to AstraZeneca standard processes.

The "Medically Important" serious criterion should be used if no other serious criteria apply.

As there is no alternative explanation for the HL case, a causality assessment of "related" should be assigned.

If there is an unavoidable delay of over 3 weeks in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term "Potential Hy's Law") applying serious criteria and causality assessment as per above
- Continue follow-up and review according to the agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review.

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

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

At the first on-study treatment occurrence of PHL criteria being met, the Investigator will:

- Determine if there has been a significant change in the patients' condition compared with the last visit where PHL criteria were met.

If there is no significant change, no action is required.

If there is a significant change, notify the AstraZeneca representative, who will inform the central Study Team, then follow the subsequent process described in Potential Hy's Law criteria met of this appendix.

A "significant" change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator; this may be in consultation with the Study Physician if there is any uncertainty.

Actions Required for Repeat Episodes of Potential Hy's Law

This section is applicable when a patient meets PHL criteria on study treatment and has already met PHL criteria at a previous on-study treatment visit.

The requirement to conduct follow-up, review, and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The Investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

- Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study, eg, chronic or progressing malignant disease or severe infection or liver disease, or did the patient meet PHL criteria prior to starting study treatment and at their first on-study treatment visit as described in Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment?

If No: follow the process described in Potential Hy's Law criteria met of this appendix.

If Yes:

Determine if there has been a significant change in the patient's condition compared with when PHL criteria were previously met.

- If there is no significant change, no action is required.
- If there is a significant change, follow the process the subsequent process described in Potential Hy's Law criteria met of this appendix.
- A "significant" change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator; this may be in consultation with the Study Physician if there is any uncertainty.

References

FDA Guidance for Industry. Drug-induced liver injury: premarketing clinical evaluation. Issued July 2009. Available from: URL: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

APPENDIX F GUIDELINES FOR EVALUATION OF OBJECTIVE TUMOR RESPONSE USING RECIST 1.1 CRITERIA (RESPONSE EVALUATION CRITERIA IN SOLID TUMORS)

1. INTRODUCTION

This appendix details the implementation of Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1) guidelines (Eisenhauer et al 2009) for the D419QC00002 study with regard to Investigator assessment of tumor burden including protocol-specific requirements for this study.

2. DEFINITION OF MEASURABLE, NON-MEASURABLE, TARGET, AND NON-TARGET LESIONS

Patients with at least 1 target lesion (tumor) that can be accurately assessed at baseline on images from computed tomography (CT) or magnetic resonance imaging (MRI) should be included in this study.

2.1. Measurable

A lesion, not previously irradiated prior to first IP administration, that can be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes, which must have short axis[1] ≥15 mm) with CT or MRI and that is suitable for accurate repeated measurements.

2.2. Non-measurable

- All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis at baseline[2]).
- Truly non-measurable lesions include the following: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by CT or MRI.

[1] The short axis is defined as the longest axis perpendicular to the long axis of the tumor.
[2] Lymph nodes with <10 mm short axis are considered non-pathological and should not be recorded or followed as non-target lesions (NTLs).

- Previously irradiated lesions[3]
- Skin lesions assessed by clinical examination
- Brain metastasis

2.3. Special cases

- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, can be considered measurable if the soft tissue component meets the definition of measurability. Blastic lesions are considered non-measurable.
- Cystic metastases can be considered measurable lesions if they meet the criteria for measurability from a radiological point of view, but if non-cystic lesions are present in the same patient, these should be selected as target lesions (TLs).

2.4. Target lesions

A maximum of 5 measurable lesions (with a maximum of 2 lesions per organ), representative of all lesions involved suitable for accurate repeated measurement, should be identified as TLs at baseline. A bilateral organ, eg, adrenal glands, is considered as a single organ. Lymph nodes, in any location, are collectively considered as a single organ, with a maximum of 2 lymph nodes as TLs.

2.5. Non-target lesions

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline.

3. METHODS OF ASSESSMENT

The same method of assessment (imaging modality), anatomical coverage, and imaging technique (eg, reconstruction interval: slice thickness, gap) should remain consistent across all imaging visits for any given patient.

A summary of the methods to be used for RECIST 1.1 assessment is provided in Appendix F Table 1 below, and those excluded from tumor assessments for this study are highlighted with the rationale provided.

[3] Localized post-radiation changes that affect lesion sizes may occur. Therefore, lesions that have been previously irradiated will not be considered measurable and should be selected as NTL at baseline and followed up as part of the NTL assessment.

Appendix F Table 1 Summary of methods of assessment

Target lesions	Non-target lesions	New lesions
CT (preferred modality; preferably with IV contrast)	CT (preferred modality; preferably with IV contrast)	CT (preferred modality; preferably with IV contrast)
MRI (preferably with IV contrast)	MRI (preferably with IV contrast)	MRI (preferably with IV contrast)
	Clinical examination	Clinical examination
	X-ray, chest X-ray	X-ray, chest X-ray
		Ultrasound
		Bone scan
		FDG-PET

Note: MRI with IV contrast is preferred modality over CT with IV contrast for brain imaging.
CT Computed tomography; FDG-PET fluorodeoxyglucose positron emission tomography; IV Intravenous; MRI: Magnetic resonance imaging.

The following are scanning options in decreasing order of preference:

1. Chest-abdomen CT with intravenous (IV) contrast administration

2. Chest CT without IV contrast administration + abdomen MRI with gadolinium IV contrast, only if iodine contrast media are medically contraindicated at any time during the study

3. Chest-abdomen CT without IV contrast

3.1. CT and MRI

CT and MRI, each preferably with IV contrast, are generally considered to be the best currently available and reproducible methods to measure TL selected for response assessment and to assess NTL and identification of any new lesions.

In this study, it is recommended that IV contrast-enhanced CT examinations of the chest and abdomen (including liver and adrenal glands) will be used to assess tumor burden at baseline and follow-up visits. In patients who are sensitive to IV CT contrast, a non-contrast CT examination of the chest and an MRI with IV contrast of the abdomen are appropriate. For brain lesion assessment, MRI with IV contrast is the preferred method over contrast-enhanced CT. It is strongly recommended to maintain use of the same imaging modality (CT or MRI), acquisition protocol, facility, and scanner across all imaging timepoints per patient.

3.2. Clinical examination

In this study, clinical examination will not be used for assessment of TL. Clinically detected lesions can be selected as TLs if they are assessed by CT or MRI scans. Clinical examination can be used to assess NTLs in patients who also have other lesions assessable by CT, MRI, or plain X-ray and to identify the presence of new lesions.

3.3. X-ray

Chest X-ray

In this study, chest X-ray assessment will not be used for assessment of TL as they will be assessed by CT or MRI examination. Chest X-ray can, however, be used to assess NTL and to identify the presence of new lesions.

Plain X-ray

In this study, plain X-ray may be used as a method of assessment for bone NTL and to identify the presence of new bone lesions.

3.4. Ultrasound

In this study, ultrasound examination will not be used for assessment of TL and NTL, as it is not a reproducible method, does not provide an accurate assessment of tumor size, and it is subjective and operator dependent. Ultrasound examination can, however, be used to identify the presence of new lesions. If new clinical symptoms occur and an ultrasound is performed, then new lesions should be confirmed by CT or MRI examination.

3.5. Endoscopy and laparoscopy

In this study, endoscopy and laparoscopy will not be used for tumor assessments because they are not validated in the context of tumor assessment.

3.6. Tumor markers

In this study, tumor markers will not be used for tumor response assessments per RECIST 1.1.

3.7. Cytology and histology

In this study, histology will not be used as part of the tumor response assessment as per RECIST 1.1.

Cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment is required when the measurable tumor has met criteria for response or stable disease. In such circumstances, the cytology is necessary for the Investigator to differentiate between response/stable disease (an effusion may be a side effect of the treatment) and progressive disease (if the neoplastic origin of the fluid is confirmed). Where cytology findings are not available, any effusion that significantly worsens (from trace to large) or appearance of clinically significant effusion (requiring change in drug therapy) during the study treatment will be considered to be progression of NTL or disease progression due to new lesions.

3.8. Isotopic bone scan

Bone lesions identified on an isotopic bone scan at baseline and confirmed by CT, MRI, or Xray- at baseline should be recorded as NTL and followed by the same method as per baseline assessment.

In this study, isotopic bone scans may be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. New lesions will be recorded where a positive hot spot that was not present on the baseline bone scan assessment is identified on a bone scan performed at any time during the study. The Investigator should consider the positive hot spot to be a significant new site of malignant disease and represent true disease progression in order to record the new lesion. Confirmation by CT, MRI, and Xray- is recommended where bone scan findings are equivocal.

3.9. FDG-PET scan

^{18}F-FDG-PET (fluorodeoxyglucose positron emission tomography) scans may be used as a method for identifying new lesions, according with the following algorithm: New lesions will be recorded where there is positive FDG uptake[4] not present on baseline ^{18}F-FDG-PET scan or in a location corresponding to a new lesion on CT/MRI at the same follow-up visit. If there is no baseline ^{18}F-FDG-PET scan available, and no evidence of new lesions on CT/MRI scans, then follow-up CT/MRI assessments should be continued, scheduled as per protocol or clinical indicated, in order to confirm new lesions.

4. TUMOR RESPONSE EVALUATION

4.1. Schedule of evaluation

The methods of assessment of tumor burden used at baseline CT/MRI scans, preferably with IV contrast, of the chest and abdomen (including liver and adrenal glands) must be used at each subsequent follow-up assessment. Additional imaging may be performed based on the signs and symptoms of the patient (eg, new lesions at follow-up).

Efficacy for all patients (all cohorts) will be assessed on images collected on visits as described in the corresponding appendix until confirmed objective disease progression or off study. It is important to follow the assessment schedule as closely as possible (refer to the study plans in each arm [screening and treatment period, and follow-up]). If an unscheduled imaging assessment is performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at his or her next regularly scheduled imaging visit.

A follow up scan should be collected for all patients following a prior timepoint with an overall assessment of complete response (CR), partial response (PR), or progressive disease (PD) by RECIST 1.1. The follow up scan should occur preferably at the next scheduled visit and no earlier than 4 weeks after the prior assessment of CR, PR, or PD, respectively.

[4] A positive FDG-PET scan lesion should be reported only when uptake is greater than approximately twice that of the surrounding tissue or liver.

4.2. Target lesions

4.2.1. Documentation of target lesions

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes collectively considered as a single organ) and representative of all lesions involved, should be identified as TLs at baseline. Target lesions should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis for nodal lesions) but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

The site and location of each TL should be documented as well as the longest diameter for non-nodal lesions (or short axis for lymph nodes). All measurements should be recorded in millimeters. At baseline, the sum of the diameters for all TLs will be calculated and reported as the baseline sum of diameters. At follow-up visits, the sum of diameters for all TLs will be calculated and reported as the follow-up sum of diameters.

4.2.2. Special cases

- For TL measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis.
- If the CT/MRI slice thickness used is >5 mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.
- If a lesion has completely disappeared, the longest diameter should be recorded as 0 mm.
- If a TL splits into 2 or more parts, then record the sum of the diameters of those parts.
- If 2 or more TLs merge, then the sum of the diameters of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion(s).
- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5 mm.
- If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion.
- When a TL has had any intervention (eg, radiotherapy, embolization, or surgery) during the study, the size of the TL should still be provided where possible.

4.2.3. Evaluation of target lesions

This section provides the definitions of the criteria used to determine objective tumor visit response for TL (see Appendix F Table 2 below).

Appendix F Table 2 Evaluation of TLs

Complete response	Disappearance of all TLs since baseline. Any pathological lymph nodes selected as TLs must have a reduction in short axis to <10 mm.
Partial response	At least a 30% decrease in the sum of the diameters of TL, taking as reference the baseline sum of diameters
Stable disease	Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progression of disease
Progression of disease	At least a 20% increase in the sum of diameters of TLs, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.
Not evaluable	Only relevant if any of the TLs were not assessed or not evaluable or had a lesion intervention at this visit. *Note:* if the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a TL response

TL Target lesion.

4.3. Non-target lesions

Evaluation of non-target lesions

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits. At each visit, an overall assessment of the NTL response should be recorded by the Investigator. This section provides the definitions of the criteria used to determine and record overall response for NTL at the investigational site at each visit (see Appendix F Table 3).

Appendix F Table 3 Evaluation of non-target lesions

CR	Disappearance of all NTLs since baseline. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non-CR/Non-PD	Persistence of one or more NTL.
PD	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in 1 lesion only or in several lesions. In all cases, the progression MUST be clinically significant for the physician to consider changing or stopping therapy.
NE	Only relevant when one or some of the NTLs were not assessed and, in the Investigator's opinion, they are not able to provide an evaluable overall NTL assessment at this visit. *Note:* for patients without TLs at baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met.

CR: complete response; NE: not evaluable; NTL: Non-target lesion; PD; progression; TL: Target lesion.

To achieve "unequivocal progression" on the basis of NTLs, there must be an overall level of substantial worsening in non-target disease such that, even in presence of stable disease or PR in TLs, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of 1 or more NTLs is usually not sufficient to qualify for unequivocal progression status.

4.4. New lesions

Details of any new lesions will also be recorded with the date of assessment. The presence of 1 or more new lesions is assessed as progression.

A lesion identified at a follow-up assessment in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

The finding of a new lesion should be unequivocal, ie, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor.

If a new lesion is equivocal, for example because of its small size, the treatment and tumor assessments should be continued until the new lesion has been confirmed. If repeat scans confirm there is a new lesion, then the progression date should be declared using the date of the initial scan.

4.5. Symptomatic deterioration

Symptomatic deterioration is not a descriptor of an objective response: it may be a reason for stopping study therapy.

Patients with "symptomatic deterioration" requiring discontinuation of treatment without objective radiographic evidence of disease progression at that time should continue to undergo regularly scheduled tumor assessments until objective disease progression is observed or death occurs (whichever comes first).

4.6. Evaluation of overall visit response and best overall response

The overall visit response will be derived using the algorithm shown in Appendix F Table 4.

Appendix F Table 4 Overall visit response

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	NA	No	CR
NA	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	NE	No	PR
PR	Non-PD or NE	No	PR
SD	Non-PD or NE	No	SD
NA	Non-CR/Non-PD	No	SD (Non-CR/non-PD)
NE	Non-PD or NE	No	NE
NA	NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease; NE: Not evaluable; NA: Not applicable (relevant when no TLs/NTLs at baseline); NTL: Non-target lesion; TL: Target lesion.

5. CONFIRMATION OF PROGRESSION

In this study, a confirmatory scan is required for all patients enrolled into arm A (durvalumab + tremelimumab) following the prior demonstration of PD. The confirmatory scan should occur preferably at the next scheduled visit and no earlier than 4 weeks following the date the criteria for response were first met or after the prior assessment of PD.

Confirmation of progression guidelines are set for the following reasons:

- for patient management and treatment decisions
- in the absence of significant clinical deterioration, to promote the collection of additional scans after the first radiologic RECIST 1.1 assessment of progressive

disease (PD) in order to distinguish pseudoprogression from true radiologic progression, also known as RECIST 1.1 modified for confirmation of progression

Confirmed objective disease progression refers to either of the following scenarios: 1. clinical progression/deterioration confirmed by a radiologic scan if clinically feasible; or 2. in the absence of significant clinical deterioration, radiologic PD by RECIST 1.1 followed by a second radiologic confirmation scan with PD assessed according to the specific confirmation of progression criteria listed below. RECIST 1.1 modified for confirmation of progression refers to the second scenario above. The confirmatory scan should occur preferably at the next scheduled imaging visit and no earlier than 4 weeks following the date of the immediate prior assessment of RECIST 1.1 PD.

Immediate prior radiologic progression would be considered confirmed if any the following criteria are met in the confirmatory scan:

- ≥20% increase in the sum diameters of TLs compared with the nadir at 2 consecutive visits, with an absolute increase of at least 5 mm in sum of diameters compared to nadir,

- and/or significant progression (worsening) of NTLs and/or of pre-existing new lesions at the confirmatory scan time-point compared with the immediate prior time-point (Note: Pre-existing new lesions are evaluated as NTLs at the confirmatory scan time-point),

- and/or additional new unequivocal lesions at the confirmatory scan time-point.

NOTE: In order to have confirmed objective disease progression, there should be two consecutive PD's, the first PD by RECIST 1.1 and the second PD using the confirmation of progression criteria (above). If the first PD by RECIST 1.1 is not confirmed, continue with assessments until the next PD by RECIST 1.1, which in turn will need its own immediate subsequent confirmation scan.

In the absence of significant clinical deterioration, treatment with study drug may continue between the initial assessment of progression and the scan to confirm progression.

If the confirmation scan confirms progression, then the date of the prior scan with PD should be declared as the date of progression.

If progression is not confirmed, in the absence of significant clinical deterioration, then the patient should continue study drug and on-treatment assessments until the next PD which will also require a follow-up confirmation scan. **If the first PD is not confirmed by the immediate next scan, then the Investigator should not change the PD assessment of the first scan**.

If a patient discontinues treatment (and/or receives a subsequent anticancer therapy) prior to radiologic progression, then the patient should still continue to be followed until confirmed objective disease progression.

Patients will also be assessed every 6/8 weeks ± 1 week (please check applicable appendix for details) for a second progression defined according to local standard clinical practice and may involve any objective radiological, symptomatic progression, or death.

6. SPECIFICATIONS FOR RADIOLOGICAL IMAGING

The use of standardized protocols for CT and MRI allows comparability both within and between different studies, irrespective of where the examination has been undertaken. It is strongly recommended to maintain use of the same imaging modality (CT and/or MRI), acquisition protocol, facility, and scanner across all imaging timepoints per patient.

6.1. CT scan

CT scans should be contiguous throughout all the anatomical regions of interest. In this study, it is recommended that CT examinations of the chest and abdomen (including liver and adrenal glands), preferably with IV contrast, will be used to assess tumor burden.

The most critical CT image acquisition parameters for optimal tumor evaluation using RECIST 1.1 are anatomic coverage, contrast administration, slice thickness, and reconstruction interval.

6.1.1. Anatomic coverage

Optimal anatomic coverage for most solid tumors is the chest, abdomen, and pelvis (chest and abdomen in this study). Coverage should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients. Because a lesion later identified in a body part not scanned at baseline would be considered as a new lesion representing disease progression, careful consideration should be given to the extent of imaging coverage at baseline and at subsequent follow-up timepoints. This will enable better consistency not only of tumor measurements but also identification of new disease.

6.1.2. Intravenous contrast administration

Optimal visualization and measurement of metastases in solid tumors require consistent administration (dose and rate) of intravenous contrast as well as timing of scanning. Typically, most abdominal imaging is performed during the portal venous phase and (optimally) is about the same time frame after injection on each examination. An adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient. It is very important that the same technique be used at baseline and on follow-up examinations for a given patient. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) should be performed should also be based on the tumor type and anatomic location of the disease and should be optimized to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other

approaches is possible, and if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of TLs on a different modality and interpretation of non-target disease or new lesions since the same lesion may appear to have a different size using a new modality. Oral contrast is recommended to help visualize and differentiate structures in the abdomen.

If iodine contrast media are medically contraindicated at baseline or at any time during the course of the study, then the recommended methods are CT thoracic examination without contrast and abdominal (and pelvic) MRI with contrast. If MRI cannot be performed, then CT without intravenous contrast is an option for the thorax, abdomen, and pelvic examinations. For assessment of brain lesions, MRI is the preferred method.

6.1.3. Slice thickness and reconstruction material

It is recommended that CT scans be performed at 5-mm contiguous slice thickness, and this guideline presumes a minimum 5-mm thickness in recommendations for the measurable lesion definition. Exceptionally, particular institutions may perform medically acceptable scans at slice thicknesses greater than 5 mm. If this occurs, the minimum size of measurable lesions at baseline should be twice the slice thickness of the baseline scans.

All window settings should be included in the assessment, particularly in the thorax where lung and soft tissue windows should be considered. When measuring lesions, the TLs should be measured on the same window setting for repeated examinations throughout the study. All images from each examination should be included in the assessment and not "selected" images of the apparent lesion.

6.2. MRI scan

MRI has excellent contrast and spatial and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. The modality used at follow-up should be the same as was used at baseline, and the lesions should be measured/assessed on the same pulse sequence. Generally, axial imaging of the abdomen and pelvis with T1 and T2 weighted imaging along with gadolinium-enhanced imaging should be performed. The field of view, matrix, number of excitations, phase encode steps, use of fat suppression, and fast sequences should be optimized for the specific body part being imaged as well as the scanner used. It is beyond the scope of this appendix to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used, and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques if possible. For these reasons, CT is the imaging modality of choice.

6.3. CT portion of PET/CT scans

At present, low dose or attenuation correction CT portions of a combined positron emission tomography (PET)/CT are of limited use in anatomically based efficacy assessments and it is therefore suggested that they should not substitute for dedicated diagnostic contrast-enhanced

CT scans for tumor measurements by RECIST 1.1. In exceptional situations, if a site can document that the CT performed as part of a PET/CT is of identical diagnostic quality (with IV iodine-based CT contrast) to a dedicated diagnostic CT, then the CT portion of the PET/CT can be used for RECIST measurements. However, this is not recommended because the PET portion of the CT introduces additional (PET) data that may bias an Investigator if it is not routinely or serially performed.

APPENDIX G DEFINITION OF WOMEN OF CHILDBEARING POTENTIAL AND ACCEPTABLE CONTRACEPTIVE METHODS

1. DEFINITION OF WOCBP AND WOMEN NOT OF CHILDBEARING POTENTIAL

- Women of childbearing potential:

  Women between menarche and menopause who have not been permanently or surgically sterilized and are capable of procreation.

- Women not of childbearing potential:

  Women who are permanently or surgically sterilized or post-menopausal (definitions below):

  Permanent sterilization includes hysterectomy and/or bilateral oophorectomy and/or bilateral salpingectomy but excludes bilateral tubal occlusion. Tubal occlusion is considered a highly effective method of birth control but does not absolutely exclude possibility of pregnancy (the term occlusion refers to both occluding and ligating techniques that do not physically remove the oviducts).

  Women who have undergone tubal occlusion should be managed on trials as if they are of WoCBP (eg, undergo pregnancy testing etc, as required by the study protocol).

- Women will be considered post-menopausal if they are amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

  Women under 50 years old will be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and with LH and FSH levels in the post-menopausal range.

  Women over 50 years of age will be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments.

2. ACCEPTABLE CONTRACEPTION METHODS

Highly effective method of birth control is defined in Note 3 in ICH Guidance M3 (Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals) as one that results in a low failure rate (eg, <1% per year) when used consistently and correctly.

Note that women should have been stable on their chosen method of birth control for a minimum of 2 weeks before entering the trial. Generic names and examples of trade names are given. As trade names may vary, investigators should check the generic name of any contraception to ensure suitability.

Acceptable Non-hormonal birth control methods include:

- Vasectomised sexual partner PLUS male condom. With participant assurance that partner received post-vasectomy confirmation of azoospermia.
- Total sexual abstinence. Abstinence must continue for the total duration of study treatment and for at least 1 month after the last dose for female study subjects, and for 6 months after last dose for male study subjects. Periodic abstinence (eg, calendar ovulation, symptothermal post ovulation methods) and withdrawal are not acceptable methods of contraception.
- Tubal occlusion PLUS male condom
- Intra-uterine Device (IUD) - provided coils are copper-banded plus male condom

Acceptable hormonal methods:

- Normal and low dose combined oral pills PLUS male condom
- Cerazette (desogestrel) PLUS male condom. Cerazette is currently the only highly efficacious progesterone based pill.
- Hormonal shot or injection (eg., Depo-Provera) PLUS male condom
- Etonogestrel implants (e.g., Implanon, Norplant) PLUS male condom
- Norelgestromin / ethinylestradiol transdermal system PLUS male condom
- Intrauterine system [IUS] device (eg., levonorgestrel releasing IUS -Mirena®) PLUS male condom
- Intravaginal device (e.g., ethinylestradiol and etonogestrel) PLUS male condom
- Cerazette (desogestrel) plus male condom. Cerazette is currently the only highly efficacious progesterone based pill

The following methods are considered not to be highly effective and are therefore not acceptable contraceptive methods in AstraZeneca clinical trials:

- Triphasic combined oral contraceptives (COCs)
- All progesterone only pills except Cerazette
- All barrier methods, if intended to be used alone
- Non-copper containing Intra-Uterine Devices (IUDs)

- Fertility awareness methods
- Coitus interruptus

APPENDIX H ADDITIONAL SAFETY INFORMATION

Further Guidance on the Definition of a Serious Adverse Event (SAE)

Life threatening

"Life-threatening" means that the patient was at immediate risk of death from the adverse event (AE) as it occurred or it is suspected that use or continued use of the product would result in the patient's death. "Life-threatening" does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalization

Outpatient treatment in an emergency room is not in itself a serious adverse event (SAE), although the reasons for it may be (eg, bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalization, disability, or incapacity but may jeopardize the patient or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring intravenous hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion, etc) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

A Guide to Interpreting the Causality Question

When making an assessment of causality, consider the following factors when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the patient actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?

- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, other host, or environmental factors.

- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?

- Is there a known mechanism?

Causality of "related" is made if, following a review of the relevant data, there is evidence for a "reasonable possibility" of a causal relationship for the individual case. The expression "reasonable possibility" of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as "not related."

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility

APPENDIX I DISALLOWED MEDICATIONS AND MEDICATIONS TO BE ADMINISTERED WITH CAUTION

In addition to any prohibited medications described in the individual arm sub protocol, any other drugs should be avoided at the Investigator's discretion if, in their opinion, the co-administration with study products may increase the risk of a clinically significant drug interaction.

A list of the main CYP3A4 substrates strong, moderate, and weak inhibitors, and strong and moderate and weak inducers, CYP2C19 substrates, P-gp substrates and inhibitors, BCRP substrates and drugs with a known risk of Torsades de pointes are shown below. This is not an exhaustive list and further details can be found at Expert Opin. Drug Metab. Toxicol. (2013) 9(6):737-751

Appendix I CYP3A4 Inhibitors

Strong	Moderate	Weak	
Boceprevir	ACT-178882	Almorexant	Isoniazid
Clarithromycin	Amprenavir	Alprazolam	Ivacaftor
Cobicistat (GS-9350)	Aprepitant	AMD070	Lacidipine
Conivaptan	Atazanavir	Amiodarone	I Linagliptin
Danoprevir	Casopitant	Amlodipine	Lomitapide
Elvitegravir	Ciprofloxacin	Atorvastatin	M100240
Fosamprenavir	Crizotinib	Azithromycin	Nilotinib
Grapefruit juice	Darunavir	Berberine	Oral contraceptives
Idelalisib	Dronedarone	Bicalutamide	Pazopanib
Indinavir	Diltiazem	Blueberry juice	Peppermint oil
Itraconazole	Erythromycin	Chlorzoxazone	Propiverine
Ketoconazole	FK1706	Cilostazol	Ranitidine
LCL161	Fluconazole	Cimetidine	Ranolazine
Lopinavir	Fosamprenavir	Clotrimazole	Resveratrol
Mibefradil	Imatinib	Cranberry juice	Roxithromycin
Nefazodone	Ledipasvir	Cyclosporine	Seville orange juice
Nelfinavir	Lomitapide	Daclatasvir	Simeprevir
Posaconazole	Netupitant	Delavirdine	Sitaxentan

Appendix I CYP3A4 Inhibitors

Strong	Moderate	Weak	
Ritonavir	Schisandra sphenanthera	Everolimus	Suvorexant
Saquinavir	Tofisopam	Faldaprevir	Tabimorelin
Telaprevir	Verapamil	Fluvoxamine	Tacrolimus
Telithromycin		Fosaprepitant (IV)	Teriflunomide
Tipranavir		Ginkgo	Ticagrelor
Troleandomycin		Goldenseal	Tipranavir/ritonavir
Voriconazole		GSK1292263	Tolvaptan
		GSK2248761	Zileuton

Appendix I CYP3A4 Inducers

Strong and Moderate	Weak	
Avasimibe	Amprenavir	PA-824
Bosentan	Aprepitant	Pleconaril
Carbamazepine	Armodafinil	Prednisone
Efavirenz	AZD 7325	Quercetin
Enzalutamide	Bexarotene	Raltegravir
Etravirine	Boceprevir	Ritonavir
Genistein	Brivaracetam	Rufinamide
Lersivirine	Clobazam	Sorafenib
Lopinavir	Danshen	Stribild
Mitotane	Dexamethasone	Telaprevir
Modafinil	Echinacea	Terbinafine
Nafcillin	Eslicarbazepine	Ticagrelor
Phenobarbital	Garlic	Ticlopidine
Phenytoin	Gingko	Topiramate
Rifabutin	Ginseng	Troglitazone
Rifampin	Glycyrrhizin	Vemurafenib
Ritonavir	LCL161	Vicriviroc and ritonavir
Semagacestat	Methylprednisolone	Vinblastine
St John's Wort	Nevirapine	
Thioridazine	Oritavancin	

Appendix I CYP3A4 Inducers

Strong and Moderate	Weak
Tipranavir	Oxcarbazepine

Appendix I CYP3A and CYP3A4 Sensitive Substrates or Substrates with a Narrow Therapeutic Range

ABT-384	osphamide	Ifosfamide	Quetiapine
Alfentanil	Cyclosporine	Imatinib	Quinidine
Aprepitant	Danoprevir	Indinavir	Ranolazine
Alfuzosin	Darifenacin	Ironotecan	Ridaforolimus
Almorexant	Darunavir	Ivacaftor	Romidepsin
Alpha-Dihydroergocryptine	Dasatinib	Ixabepilone	Saquinavir
Amiodarone	Dihydroergotamine	L-771,688	Sildenafil
Aplaviroc	Disopyramide	Lapatinib	Simeprevir
Aprepitant	Dronedarone	Levomethadyl (LAAm)	Simvastatin
Astemizole	Docetaxol	Lomitapide	Sirolimus
Atazanavir	Dofetilide	Lopinavir	Tacrolimus
Atorvastatin	Doxorubicin	Lovastatin	Temsirolimus
Avanafil	Ebastine	Lurasidone	Terfenadine
Bexarotine	Eletriptan	Maraviroc,	Ticagrelor
BIRL 355	Elvitegravir	Midazolam	Theoophylline
Bortezomib	Eplerenone	Midostaurin	Thioridazine
Bosutinib	Ergotamine	Mosapride	Thiotepa
Brecanavir	Erlotinib	Neratinib	Tilidine
Brotizolam	Etoposide	Nilotinib	Tipranavir
Budesonide	Everolimus	Nisoldipine	Tolvaptan
Buspirone	Felodipine	Paclitaxel	Triazolam
Capravirine	Fentanyl	Pazopanib	Tretinoin
Carbamazepine	Fluticasone	Perospirone	Ulipristal
Casopitant	Gefitinib	Pimozide	Vardenafil
Cisapride	Halofantrine	Propafenone	Vicriviroc
Conivaptan	Ibrutinib	Propofol	Voclosporin

Appendix I CYP2C19 Sensitive Substrates or Substrates with a Narrow Therapeutic Range

Diazepam	Gliclazide	Lansoprazole
(R)-Lansoprazole	(S)-Lansoprazole	(S)-Mephenytoin
(R)-Mephobarbital	Omeprazole	(R)-Omeprazole
Pantoprazole	(+)-Pantoprazole	Rabeprazole
Tilidine		

Appendix I CYP1A2 Sensitive Substrates or Substrates with a Narrow Therapeutic Range

Alosetron	Caffeine	Duloxetine
Melatonin	Ramelteon	Tacrine
Theophylline	Tizanidine	

Appendix I P-gp Substrates

Colchicine	Digoxin	Fexofenadine
Indinavir	Paclitaxel	Toptecan
Vincristine		

If a patient requires initiation of digoxin during the study, or is already receiving treatment with digoxin, monitoring of digoxin levels is recommended according to local practice (as the levels of digoxin may increase). Monitoring of digoxin levels is also recommended when the patient has completed dosing with study treatment (as the levels of digoxin may then decrease).

Appendix I P-gp Inhibitors (Strong)

Cyclosporine	Elacridar	Erythromycin
Itraconazole	Ketocoanzole	LY335979Quinidine
Ritonavir	Valspodar	Verapamil

Appendix I BCRP Substrates

Daunorubicin	Doxorubicin	Rosuvastatin
Sulfasalazine	Topotecan	

Appendix I Medicines with a known risk of Torsades de pointes

Amiodarone	Disopyramide	Ibogaine	Probucol

Anagrelide	Dofetilide	Ibutilide	Procainamide
Arsenic trioxide	Domperidone	Levofloxacin	Propofol
Astemizole	Donepezil	Levomepromazine	Quinidine
Azithromycin	Dronedarone	Levomethadyl acetate	Roxithromycin
Bepridil	Droperidol	Levosulpiride	Sevoflurane
Chloroquine	Erythromycin	Mesoridazine	Sotalol
Chlorpromazine	Escitalopram	Methadone	Sparfloxacin
Cilostazol	Flecainide	Moxifloxacin	Sulpiride
Ciprofloxacin	Fluconazole	Ondansetron	Sultopride
Cisapride	Gatifloxacin	Oxaliplatin	Terfenadine
Citalopram	Grepafloxacin	Papaverine HCl	Thioridazine
Clarithromycin	Halofantrine	Pentamidine	Vandetanib
Cocaine	Haloperidol	Pimozide	

Note: Medicines on this list are reviewed on an ongoing basis to assure that the available evidence supports their continued placement on this list. The list changes regularly and we recommend checking the website at crediblemeds.org for the most up-to-date information. There may be many additional brand names that are not listed on this form. Disclaimer and Waiver: The information presented is intended solely for the purpose of providing general information about health-related matters. It is not intended for any other purpose, including but not limited to medical advice and/or treatment, nor is it intended to substitute for the users' relationships with their own health care providers. To that extent, by use of this website and the information it contains, the user affirms the understanding of the purpose and releases AZCERT, Inc. from any claims arising out of his/her use of the website and its lists. The absence of drugs from these lists should not be considered an indication that they are free of risk of QT prolongation or Torsades de pointes. Many medicines have not been tested for this risk in patients, especially those with congenital long QT syndrome.

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Genetic research plan and procedures

Selection of genetic research population

Study selection record

All subjects will be asked to participate in this genetic research. Participation is voluntary and if a subject declines to participate there will be no penalty or loss of benefit. The subject will not be excluded from any aspect of the main study.

Inclusion criteria

- For inclusion in this genetic research, subjects must fulfil all of the inclusion criteria described in the main body of the Clinical Study Protocol **and**: Provide informed consent for the genetic sampling and analyses.

Exclusion criteria

Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:

- Previous allogeneic bone marrow transplant
- Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection

Withdrawal of consent for genetic research:

Subjects may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary withdrawal will not prejudice further treatment. Procedures for withdrawal are outlined in Section 6.6.6of the main Clinical Study Protocol.

Collection of samples for genetic research

The blood sample for genetic research will be obtained from the subjects at Screening Visit. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding subjects who may withdraw due to an adverse event (AE), such subjects would be important to include in any genetic analysis. If for any reason the sample is not drawn at Screening Visit, it may be taken at any visit until the last study visit. Only one sample should be collected per subject for genetics during the study. Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

Coding and storage of DNA samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain subject confidentiality. Samples will be stored for a maximum of 15 years, from the date of last subject last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

An additional second code will be assigned to the blood either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable only by the second, unique number. This number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated organisation. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organisations working with the DNA).

The link between the subject enrolment/randomisation code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organisations. The link will be used to identify the relevant DNA samples for

analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and permit tracing of samples for destruction in the case of withdrawal of consent.

Ethical and regulatory requirements
The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Section 11.

Informed consent
The genetic component of this study is optional and the subject may participate in other components of the main study without participating in the genetic component. To participate in the genetic component of the study the subject must sign and date both the consent form for the main study and the genetic component of the study. Copies of both signed and dated consent forms must be given to the subject and the original filed at the study centre. The Principal Investigator(s) is responsible for ensuring that consent is given freely and that the subject understands that they may freely withdrawal from the genetic aspect of the study at any time.

Patient data protection
AstraZeneca will not provide individual genotype results to subjects, any insurance company, any employer, their family members, general physician unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a subject's identity and also have access to his or her genetic data. In addition, Regulatory authorities may require access to the relevant files, though the subject's medical information and the genetic files would remain physically separate.

Data management
Any genotype data generated in this study will be stored at a secure system at AstraZeneca and/or designated organizations to analyse the samples.

AstraZeneca and its designated organisations may share summary results (such as genetic differences from groups of individuals with a disease) from this genetic research with other researchers, such as hospitals, academic organisations or health insurance companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can only use this information for health related research purposes. Researchers may see summary results but they will not be able to see individual subject data or any personal identifiers.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

Statistical methods and determination of sample size

The number of subjects that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A Statistical Analysis Plan may be prepared where appropriate.

APPENDIX K LIST OF REFERENCES

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