Statistical Analysis Plan	
Study Code	D8731C00001
Edition Number	2.0
Date	08/November/2021

An Open-label, Multi-drug, Multi-center Phase II Combination Study of AZD4635 in Patients with Prostate Cancer

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

No table of figures entries found.

LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
$A_{2A}R$	Adenosine 2A receptor
Ae	Amount of drug excreted unchanged
AE	Adverse event
AESI	Adverse Event of Special Interest
BoR	Best objective response
BP	Blood pressure
CCI	CCI
CL_R	Renal clearance
CRF	Case Report Form
CR	Complete response
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DCO	Data cut-off
DLT	Dose-limiting toxicity
DOR	Duration of Response
ECG	Electrocardiogram
ECHO	Echocardiograph
ECOG	Eastern Cooperative Oncology Group
EWOC	Escalation with Overdose Control
gmean	Geometric mean
GPS	Global Product Statistician
CCI	CCI
imAE	Immune mediated adverse events
CCI	CCI
IV	Intravenous
LD	Longest diameter
LOQ	Limit of quantification

Abbreviation or special term	Explanation
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
MDSC	Myeloid-derived suppressor cells
MRI	Magnetic resonance imaging
MRT	Mean residence time
MUGA	Multi-gated acquisition scan
NA	Not applicable
NC	Not calculable
NCI	National Cancer Institute
NE	Not evaluable
NK	Natural killer (cells)
NPD	Non progressive disease
NQ	Non-quantifiable
NSCLC	Non-small cell lung cancer
NTL	Non-target lesion
OAE	Other significant adverse events
ORR	Objective response rate
OS	Overall survival
PCWG	Prostate Cancer Working Group
PD	Progressive disease
CCI	CCI
CCI	CCI
PFS	Progression free survival
PID	Percentage intended dose
PK	Pharmacokinetics
PO	*Per os* (orally)
PR	Partial response
PSA	Prostate Specific Antigen
PT	Preferred term
R_{ac}	Extent of accumulation on multiple dosing
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumors

Abbreviation or special term	Explanation
rPFS	Radiological progression-free survival
QTc	QT interval corrected for heart rate
sd	Standard deviation
CCI	CCI
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
SOC	System organ class
TCP	Temporal change parameter
TL	Target lesion

AMENDMENT HISTORY

Date	Description of change	In line with the CSP?	Rationale
15 March 2021	Changed to use US English convention throughout the document.	Yes	Current protocol uses the same convention.
15 March 2021	Updated the list of abbreviations	Yes	Added a few abbreviations that were missing but being used in the SAP text.
15 March 2021	Changed the edition number.	Yes	CCI [redacted]
15 March 2021	Updated the CSP version.	Yes	To reflect the latest approved version of the CSP.
18 December 2020	Section 1.1: Updated the endpoint/ variables.	Yes	Details about radiological progression free survival variable were missing. To align with the protocol.
18 December 2020	Section 1.1: Added PK related study objective.	Yes	To align with the protocol.
18 December 2020	Section 1.1: Updated the study objectives and added CCI [redacted] evaluation.	Yes	To align with the protocol.
15 December 2020	Section 1.2: Added language in the study design section, to indicate that the analyses for module 3 will not be conducted	Yes	As per CSP version 5.0 dated 23 February 2021, overall design was amended which refers to a decision made by the sponsor not to open Module 3 to recruitment after a comprehensive strategy review of the AZD4635 program.
18 December 2020	Section 1.3: Updated section 1.3 and added 'approximately' for the number of subjects needed with measurable disease at baseline.	Yes	To align with the protocol update.
18 December 2020	Section 2.1: Updated the definition of PK analysis set in Table 2.	Yes	Discussions with PK group.

18 December 2020	Section 2.1: Changed the name of analysis set from PSA evaluable response to PSA response	Yes	To match with protocol section 9.3.
18 December 2020	Section 2.1: Updated Table 3 and added OS as one of the outcome variables.	Yes	It was missing from this table.
18 December 2020	Section 2.1: Added immunogenicity section in table 3.	Yes	To align with the protocol.
15 March 2021	Section 2.1: Updated the analysis set for PSA response in Table 3.	Yes	To be consistent with Table 2.
18 December 2020	Updated section 2.2, 4.2.2.1, and 4.2.2.3 to include Covid-19 related violations/ deviations.	Yes	The protocol was updated to capture any deviations due to Covid-19 pandemic.
10 February 2021	Section 3.1: Added description about handling of missing/ partial date for adverse events, in section 3.1,	Yes	To provide clear guidance for programming.
10 February 2021	Section 3.1: Added definition for on-treatment.	Yes	For clarity for programming.
12 February 2021	Section 3.1: Added description of handling missing AE start/ end dates.	Yes	Provide clarity to programming.
12 February 2021	Section 3.1 updated to describe visit windowing for efficacy analyses.	Yes	To provide guidance for programming of efficacy analyses.
15 March 2021	Updated the description of time windows for efficacy, in section 3.1.	Yes	To add clarity to the description of efficacy analyses.
19 March 2021	Section 3.1: Updated the description of time windows and changed the order to describe efficacy analyses first and then safety outcomes.	Yes	For better flow and clarity.
09 June 2021	Section 3.1: Removed reference to PhUSE from the subsection of ‘Missing dates’. .	Yes	The guidance for handling of partial dates is aligned with available guidance.
09 June 2021	Section 3.1: For the imputation rules for missing AE and concomitant dates, the scenarios in a, b,	Yes	To provide better programming guidance.

	and c were updated to add the condition about end date not before first dose date.		
15 June 2021	Section 3.1: Added the definition of treatment emergent adverse event.	Yes	For completeness and clear guidance for programming.
10 February2021	Updated section 3.2.1.3 and added more details on derivation of change in tumor size.	Yes	To provide clear guidance to programming and also to make sure all scenarios are included in the derivation.
15 March 2021	Updated the names of the CRF modules for 'Missed or forgotten doses' and 'Patients who permanently discontinue during a dose interruption', in section 3.4.1.	Yes	To align with the study CRF module names.
12 February 2021	Section 3.4.1 updated : clarification on calculation of total treatment duration for Oleclumab added; calculation of duration of treatment starting dose added.	Yes	To align with the AZ standard summary for duration of exposure.
12 February 2021	Section 3.4.1: Description for missed or forgotten doses updated .	Yes	Align with the current CRFs and the CRF completion guidelines.
10 February 2021	Added clarification about the use of snapshot date and/ or DCO date in section 3.4.1.	Yes	For clearer guidance to programming.
15 March 2021Section	Details added in Section 3.4.2 about different doses administered for AZD4635, for module 2..	Yes	To add clarity and align with the CSP.
10 February 2021	Added description for handling of immune mediated adverse events, in section 3.4.3.	Yes	As per the prevailing guidance.
18 December 2020	Added description for reporting of AESIs in section 3.4.3.	Yes	To align with the protocol.
16 July 2021	Section 3.4.4: Updated the description for ECG schedule and programming instructions.	Yes	Better reflect the details in the protocol.
16 July 2021	Section 3.4.5: Added this section about ECHO/ MUGA.	Yes	To align with the protocol.

16 July 2021	Section 3.4.6: Added the description for the vital signs collection routine.	Yes	To align with protocol.
16 July 2021	Section 4.2.2: Added the description for the summary of study disruptions due to COVID-19 pandemic.	Yes	To align with the mandated outputs per AZ guidance on reporting Covid-19 related disruptions.
12 February 2021	Section 4.2.2.7 was updated to remove the description of handling of partial dates.	Yes	To adhere to the PhUse language for the imputation of missing/ partial dates for AEs and concomitant medications.
15 March 2021	Section 4.2.2.7, removed the post treatment medication definition with start date of 30 days after the last dose pf AZD4635.	Yes	This information was conflicting with the other definition of post-treatment medication.
30 June 2021	Section 4.2.2.8: Added details about the listing for medical history.	Yes	The listing was missing and was requested to be added by the medical writing team.
15 December2020	Section 4.2.3.1: Added calculation of 80% CI based on Clopper-Pearson method, for ORR	Yes	To better match with decision criteria
15 March 2021	In section 4.2.3.2, removed the description of the spider plots when patients have lymph node regression.	Yes	Not needed for creating the spider plots.
June 30 2021	Section 4.2.3.2: Clarified about imputation for change in tumor size calculation.	Yes	For clarity.
June 30 2021	Section 4.2.3.3: Listing of progression details added.	Yes	Required as per AZ guidance.
18 December 2020	Section 4.2.3.5 updated to add that OS will be analyzed if sufficient number of patients are available.	Yes	For clarity about the basis for OS analysis.
15 March 2021	Updated section 4.2.3.6 to indicate the analysis maybe performed, if required.	Yes	To add clarity that this is not a required analysis.

12 February 2021	Section 4.2.4 updated and handling of patients who receive subsequent anti-cancer therapy, described.	Yes	To align with the protocol and provide guidance to programming.
30 June 2021	Section 4.2.4: Added description for waterfall and spider plots for more clarity on the purpose of the plots.	Yes	To better explain the purpose of the graphs.
16 July 2021	Section 4.2.5.1: Added the description for the graph for the duration of exposure for the study treatment.	Yes	It was missing.
18 December 2020	Section 4.2.5.2: Updated this section to clarify the definition of Treatment emergent AE.	Yes	To make sure that all treatment emergent AEs are properly identified.
15 March 2021	Removed the description of imputation of dates in section 4.2.5.2.	Yes	Redundant information. The same details are provided in 'Missing dates' in section 3.1.
15 March 2021	Section 4.2.5.2 updated to change the responsible function for AESI definition.	Yes	AZ patient safety responsible for this task and not the representatives from SCDI.
19 April 2021	Clarified the AE follow up time period, in section 4.2.5.2.	Yes	To better align with the CRF completion guidelines.
30 June 2021	Section 4.2.5.5: Added description of the summary tables.	Yes	To clarify the summaries produced for the ECG data.
16 July 2021	Section 4.2.5.6: This section was added.	YEs	To align with the protocol.
16 July 2021	Section 4.2.5.7: Added further clarification on handling of the vital signs data.	Yes	To align with the protocol.
18 December 2020	Updated section 4.2.6 and removed the graphical presentation of plasma concentrations. Added to clarify handling of non quantifiable plasma concentration.	Yes	As per the input from the PK group.
18 October 2021	Added description for box plots in section 4.2.6.	Yes	To align with the TFL shells.

15 March 2021	Added clarification to section 4.2.7.	Yes	CCI [redacted]
18 October 2021	Modified the imAE section to include only one approach for identification of imAEs.	Yes	To align with the latest guidance on adjudication of imAEs.

1 STUDY DETAILS

1.1 Study objectives

Table 1 Study objectives	
Primary Objective:	**Endpoint/Variable:**
To evaluate efficacy of each combination therapy on objective response rate (ORR) for patients with measurable disease	Proportion of patients with measurable disease at baseline who have a confirmed ORR per Response Evaluation Criteria in Solid Tumors (RECIST 1.1)
To evaluate efficacy of each combination therapy on PSA response rate	PSA confirmed response is defined as the proportion of participants with a reduction in the PSA level of ≥50% from baseline to the lowest post-baseline PSA results, measured twice, at least 3 weeks apart by the Prostate Cancer Working Group 3 criteria (PCWG3)
Secondary Objectives:	**Endpoint/Variable:**
To evaluate the efficacy of each combination therapy on the proportion of patients alive and progression free at 6 months	Summaries of the Kaplan-Meier curve for radiological progression-free survival including the proportion of patients alive and radiological progression free at 6 months using RECIST 1.1 (soft tissue lesions) and PCWG3 (bone lesions)
To evaluate efficacy of each combination therapy on duration of response (DoR)	Duration of Response (DoR) is defined as the time from the date of first documented response until date of documented progression or death in the absence of disease progression
To evaluate efficacy of each combination therapy on overall survival (OS).	Overall survival is length of time from date of first dose until the date of death due to any cause.
To evaluate the pharmacokinetics (PK) of AZD4635 and its metabolites and other combination agent(s).	Steady state trough
To evaluate the immunogenicity of mAB study drug(s) in combination with AZD4635.	The proportion of patients with the presence of anti-drug antibody (ADA)
Safety Objective:	**Endpoint/Variable:**
To assess the safety and tolerability of each treatment regimen.	AEs/SAEs Physical exam and vital signs Collection of clinical chemistry/hematology parameters
Exploratory Objectives	**Endpoint/Variable:**
CCI [redacted]	CCI [redacted]
CCI [redacted]	CCI [redacted]

Table 1 Study objectives	
CCI	CCI
CCI	CCI
CCI	CCI
CCI	CCI
CCI	CCI
CCI	CCI
CCI	CCI

1.2 Study design

This is an open-label Phase II modular study in patients with prostate cancer to assess safety, efficacy, and tolerability of AZD4635 in combination with other therapeutic agents in different treatment modules. Patients will be randomized for inclusion in the initial 2 or 3 modules of AZD4635 plus durvalumab, AZD4635 plus oleclumab and AZD4635 plus durvalumab plus oleclumab. Patients will be dosed with the capsule formulation of AZD4635. The decision was made by the Sponsor not to open Module 3 (AZD4635 plus durvalumab plus oleclumab) to recruitment after a comprehensive strategy review of the AZD4635 program. Thus any reference to module 3 in this SAP shall not be taken into consideration from all analyses perspective.

1.3 Number of subjects

The study is a Phase 2a signal searching study and consists of multiple single arm cohorts under a modular protocol. There are no plans to formally compare between the cohorts and this is not part of the study objectives. The aim is to identify treatment(s) to take forward into further trial(s), as such there are no formal statistical hypothesis tests associated with the study objectives; statistical analysis of all study endpoints is descriptive.

The primary efficacy endpoint is PSA decline from baseline ≥50% (PSA50) and overall response rate (ORR) per RECIST v1.1 for patients with measurable disease at baseline. In Module 1, 2 and 3 there will be approximately 30 PSA evaluable patients in each module, and approximately 20 patients will have RECIST measurable disease at baseline in each module.

In Module 1, 2 and 3 , approximately 30 patients with and without measurable disease at baseline will be assessed for PSA50 in each module. CCI

[redacted]

In Module 1, 2 and 3 , approximately 20 patients with measurable disease at baseline will be assess for ORR in each module. CCI

[redacted]

If any of the required patients for PSA and/or ORR are not evaluable for PSA response or tumor response, respectively, they may be replaced at the sponsor's discretion.

2 ANALYSIS SETS

2.1 Definition of analysis sets

All patients who received at least one dose of study medication will be included in the safety analysis set. For the safety analysis, patients will be classified according to the dose schedule

they actually received. For the efficacy analysis (including OS), patients will be classified according to the planned dose schedule.

Details of the analysis sets are presented in Table 2 and Table 3.

Table 2 Analysis Set

Analysis Set	Definition
Enrolled	All patients who signed informed consent
Safety	All patients who received at least 1 dose of study drug.
DLT (Module 2)	The first 6 patients who complete 28 days AND receive all planned doses of oleclumab and at least 80% of AZD4635 during this time OR experience a DLT during this time.
Pharmacokinetics (PK)	All participants who received at least 1 dose of study drug with at least 1 reportable concentration.
Tumor response	Dosed patients with a baseline tumor assessment, and measurable disease at baseline.
Evaluable for Efficacy	Dosed patients with a baseline tumor assessment.
PSA response	Dosed patients with an abnormal baseline PSA (≥1ng/mL).

* Summaries of PK data will consider the subset of the PK analysis set with reportable plasma concentrations at that visit for which there are no important adverse events or protocol deviations that may impact PK at that visit.

Table 3 Summary of outcome variables and analysis sets

Outcome variable	Analysis Sets
Demography and baseline characteristics	Safety
Safety data	
Exposure	Safety
Adverse Events	Safety
Laboratory measurements	Safety
Vital Signs/ECG/Physical examination (ECOG)	Safety
ECHO/MUGA	Safety
Concomitant medications	Safety
Efficacy Data	
Best Objective Response	Tumor response and Evaluable for Efficacy
Objective Response Rate (ORR)	Tumor response
Change in tumor size	Tumor response
Duration of Response	Tumor response
Overall survival (OS)	Safety
Radiological progression-free survival (rPFS)	Evaluable for Efficacy

Outcome variable	Analysis Sets
PSA response	PSA Response
Pharmacokinetics	
Plasma Pharmacokinetic variables	PK
Immunogenicity	
Anti-Drug Antibody Response	Safety

2.2 Violations and deviations

The following general categories will be considered important protocol deviations:

Patients who deviate from key entry criteria per the CSP (Deviation 1) as below:

- Patients must have prostate cancer with histological or cytological confirmation [Inclusion criteria 4 of core CSP]
  - For module 1, 2 and 3 :
    - Histologically or cytologically confirmed metastatic CRPC [Inclusion criteria K-1, L-1 or M-1]
    - Patients must have had either orchiectomy OR be on luteinizing hormone-releasing hormone (LHRH) agonist or antagonist therapy with serum testosterone <50 ng/dL AND agree to stay on LHRH agonist or antagonist therapy during the study [Inclusion criteria K-1, L-1 or M-1]
    - Patients must have previously received and progressed on >2 lines of approved systemic therapy for mCRPC, including a second generation hormonal agent (eg, abiraterone, enzalutamide, apalutamide). [Inclusion criteria K-1, L-1 or M-1]
  - Patients must have evidence of mCRPC that progressed within 6 months prior to screening [Inclusion criteria K-1, L-1 or M-1]
  - Previously received and progressed on SOC [Inclusion criteria 5 of core CSP]
  - Patients must have not received prohibited anti-cancer therapy prior the first dose of study treatment as defined in the exclusion criteria in CSP
  - Patients with measurable diseases must have at least 1 documented lesion on either a bone scan or a computed tomography (CT)/magnetic resonance imaging (MRI) scan that can be followed for response is suitable for repeated measurement Or patients with non-measurable disease must have measurable PSA ≥1.0 ng/mL as the minimum starting level for trial entry if the confirmed rise is the only indication of progression (excluding small cell carcinoma) [Inclusion criteria 8 of core CSP]

- Patients assigned to treatment who received their assigned study treatment at an incorrect dose at more than 1 occasion or received an alternative study treatment to that which they were assigned (Deviation 2)
- Persistently missing important protocol required safety assessments (haematology, liver function test, chemistry panel and/or as per medical monitor discretion) and potentially having major impact to patient safety (clinical review on a case by case base) (Deviation 3).
- Baseline RECIST or Bone scan >28 days before start of assigned treatment (unless agreed with medical team), or no baseline RECIST 1.1 assessment on or before start of treatment and/or no baseline bone scan assessment on or before start of treatment or no baseline PSA (Deviation 4)
- Patient received study treatment but post-baseline tumor assessment scans not performed at all or major issues with scans not being performed in accordance with the protocol, or Patient met PSA baseline criteria and received study treatment but no post-baseline PSA data collection (Deviation 5)
- Patient received prohibited other anti-cancer therapy during study treatment period (Deviation 6)
- Changes to the procedures that impact the quality of the data or any circumstances that can alter the evaluation of the PK (Deviation 7).
- Met study treatment discontinuation criteria but continued study treatment and potentially had major impact to patients' safety according to clinical judgement (Deviation 8).
- Patients affected by the COVID-19 pandemic.

The categorization of these as IPDs is not automatic and will depend on duration and the perceived effect on efficacy and safety. In addition to the programmatic determination (where possible) of the deviations above, monitoring notes or summaries will be reviewed to determine any important post entry deviations that are not identifiable via programming, and to check that those identified via programming are correctly classified. For example, details of disallowed concomitant medication use will be reviewed and may be determined as important.

Patients who enrolled but did not receive study treatment will be excluded from the safety, PK and efficacy analysis sets. Missing baseline tumor assessment or missing baseline PSA, or having neither measurable disease at baseline nor meeting baseline PSA criteria will lead to exclusion from some of the efficacy analysis sets. None of the other deviations will lead to patients being excluded from the analysis sets (except for the PK analysis set, if the deviation is considered to impact upon PK). However, the impact on the primary endpoint will be assessed, and if considered necessary sensitivity analysis may be considered.

A list of all protocol deviations, including those reported by monitors, will be reviewed and decisions regarding how to handle these deviations will be documented by the study team physician, clinical pharmacology scientist and statistician prior to database lock. The final classification will be made prior to database lock.

The important protocol deviations will be listed and summarized by treatment group.

3 PRIMARY AND SECONDARY VARIABLES

3.1 General principles

Baseline measurements and change from baseline variables

Baseline will be the last non-missing value obtained prior to the first dose/administration of study medication and any information taken after first dose/administration of study medication will be regarded as post baseline information. If two visits are equally eligible to assess patient status at baseline (e.g., screening and baseline assessments both on the same date prior to first dose/administration with no washout or other intervention in the screening period), the average should be taken as the baseline value. For non-numeric laboratory tests (i.e., some of the urinalysis parameters) where taking an average is not possible, then the clinical favourite value would be taken as baseline (i.e., normal and abnormal were observed on the same date prior to first dose/administration, then normal is considered as baseline value). In the scenario where there are two assessments on Day 1, one with time recorded and the other without time recorded, the one with time recorded would be selected as baseline. Where safety data are summarized over time, study day will be calculated in relation to date of first treatment. If no value exists before the first dose/administration, then the baseline value will be treated as missing.

In all summaries, change from baseline variables will be calculated as the post treatment value minus the value at baseline. For % change from baseline, calculate:

100× (Post baseline value – Baseline value)/Baseline value

Study day will be calculated as:

Date of assessment – Date of first dose/administration of study medication +1

Study day prior to Date of first dose/administration of study medication will be calculated as follows:

Date of assessment – Date of first dose/administration of study medication

Time Windows

Time windows are defined for any presentations that summarize values by visit.

- For efficacy, the visit specific analyses such as change from baseline in target lesion size at week x, PSA response at week x, a windowing rule will be applied and will follow the protocol allowed visit window; therefore any RECIST scan performed within ± 7 days of the protocol scheduled visit will be used for that visit. The same +/- 7 days window will

be used for PSA. That is, only assessments closest to the protocolled visit day are selected for this summary, therefore unscheduled visits may be excluded.

The following conventions should apply to safety outcomes, where applicable

- The time windows should be exhaustive so that data recorded at any time point has the potential to be summarized. Inclusion within the time window should be based on the actual date and not the intended date of the visit.
- All unscheduled visit data should have the potential to be included in the summaries.
- The window for the visits following baseline will be constructed in such a way that the upper limit of the interval falls half way between the two visits (the lower limit of the first post-baseline visit will be Day 2). If an even number of days exists between two consecutive visits then the upper limit will be taken as the midpoint value minus 1 day.
- For example, the visit windows with 2 weeks between scheduled assessments are:
  - Day 15, visit window 2 – 21
  - Day 29, visit window 22 – 35
  - Day 43, visit window 36 – 49
  - Day 57, visit window 50 – 63
  - Day 71, visit window 64 – 77
  - Day 85, visit window 78 – 91
- For summaries showing the maximum or minimum values at a visit, the maximum/minimum value recorded on treatment at that visit (including within the corresponding window) will be used (regardless of where it falls in a window).
- Listings should display all values contributing to a time point for a patient.
- For visit based summaries, if there is more than one value per patient within a time window then the closest value to the scheduled visit date should be summarized, or the earlier, in the event the values are equidistant from the nominal visit date.
- The listings should highlight the value for the patient that contributed to the summary table, wherever feasible.
- Note: in summaries of extreme values all post baseline values collected are used including those collected at unscheduled visits regardless of whether or not the value is closest to the scheduled visit date.
- For summaries at a patient level, all values should be included, regardless of whether they appear in a corresponding visit based summary, when deriving a patient level statistic such as a maximum.

Missing Dates

In situations when the whole date is missing, it is more difficult to follow a general principle and these should be reviewed within the study and decided how to be handled.

Generally, the imputation of dates is used to decide if an observation is treatment emergent for adverse events or concomitant medications. The imputed dates are not advised to be used to calculate durations where the results would be less accurate.

Furthermore:-

- For missing diagnostic dates (e.g. disease diagnosis), if day and/or month are missing use 01 and/or Jan. If year is missing, put the complete date to missing.

- For missing AE and concomitant medication start dates, the following will be applied:

    a. Missing day - impute the 1st of the month unless month is the same as month of the first dose of study drug, and end date is not definitely before first dose date then impute first dose date.

    b. Missing day and month - impute 1st January unless year is the same as first dose, and end date is not definitely before first dosedate then impute first dose date.

    c. Completely missing - impute first dose date unless the end date indicates it ended prior to first dose, in which case impute the 1st January of the same year as the end date.

    d. Ensure that the new start date is sensible and should is no later than the end date.

- For missing AE and concomitant medication end dates, the following will be applied:

    a. Missing day - impute the last day of the month unless both the month and the year are the same as the End of Study Date or the primary analysis data cut-off date then impute the End of Study Date or the primary analysis data cut-off date.

    b. Missing day and month - impute 31st December unless the year is the same as the End of Study Date or the primary analysis data cut-off date then impute the End of Study Date or the primary analysis data cut-off date. Flags will be retained in the database indicating where any programmatic imputation has been applied, and in such cases, any durations would not be calculated.

    c. Completely Missing – need to look at whether the AE/medication is still ongoing before imputing a date and also when it started in relation to study drug. If the ongoing flag is missing then assume that AE is still present / medication is still being taken (i.e. do not impute a date).

- If a participant is known to have died where only a partial death date is available then the date of death will be imputed as the latest of the last date known to be alive +1 from the database and the death date using the available information provided:-
    - For Missing day only – using the 1st of the month.

- For Missing day and Month – using the 1st of January.

    a. Imputed end date should be no earlier than end date.

On treatment definition

Post-dose assessments are considered on treatment if the assessment occurred after first dose and up to and including the last dose.

Treatment emergent adverse event definition

Adverse events will be defined as treatment emergent if they begin, or worsen (by investigator report of a change in intensity), during the treatment period, i.e., starting after the first dose of therapy or within 30 days after the end of the last investigational product (90 days for the durvalumab and oleclumab.

3.2 Primary outcome variables

The primary outcome variables, which evaluate the efficacy of each combination therapy, are described in Table 3 of the Clinical Study Protocol.

3.2.1 Calculation of derivation of tumor response variables

3.2.1.1 RECIST visit responses

For all patients with measurable and non-measurable disease at baseline, the RECIST tumor response data will be used to determine each patient's visit response according to RECIST version 1.1. It will also be used to determine if and when a patient has progressed in accordance with RECIST and also their best objective response to study treatment.

Baseline radiological tumor assessments are to be performed no more than 28 days before the start of study treatment and ideally as close as possible to the start of study treatment. Tumor assessments are then performed at 6 weeks (post Cycle 1) and every 8 weeks thereafter following the start of study treatment until disease progression.

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

From the investigator's review of the imaging scans, the RECIST tumor response data will be used to determine each patient's visit response according to RECIST version 1.1. At each visit, patients will be programmatically assigned a RECIST 1.1 visit response of CR, PR, SD or PD, using the information from TLs, NTLs and new lesions and depending on the status of

their disease compared with baseline and previous assessments. If a patient has had a tumor assessment, which cannot be evaluated, then the patient will be assigned a visit response of not evaluable (NE) (unless there is evidence of progression in which case the response will be assigned as PD).

Please refer to Table 6 below for the definitions of CR, PR, SD and PD.

RECIST outcomes (i.e. PFS, ORR etc.) will be calculated programmatically for the site investigator data from the overall visit responses.

Target lesions (TLs)

Measurable disease is defined as having at least one measurable lesion, not previously irradiated, which is ≥ 10 mm in the longest diameter (LD) (except lymph nodes which must have short axis ≥ 15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) and which is suitable for accurate repeated measurements. A patient can have a maximum of 5 measurable lesions recorded at baseline with a maximum of 2 lesions per organ (representative of all lesions involved and suitable for accurate repeated measurement) and these are referred to as target lesions (TLs). If more than one baseline scan is recorded then measurements from the one that is closest and prior to first dose/administration of study medication will be used to define the baseline sum of TLs. 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.

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

Note: For patients who do not have measurable disease at entry (i.e. no TLs) but have non-measurable disease, evaluation of overall visit responses will be based on the overall NTL assessment and/or the absence/presence of new lesions (see Table 4 for further details). If a patient does not have measurable disease at baseline then the TL visit response will be not applicable (NA).

For patients with no disease at baseline (i.e. no TLs and no NTLs), evaluation of overall visit responses will be based on absence/presence of new lesions. If no TLs and no NTLs are recorded at a visit, both the TL and NTL visit response will be recorded as NA and the overall visit response will be no evidence of disease (NED). If a new lesion is observed then the overall visit response will be PD.

Table 4 TL visit responses

Visit Reponses	Description
Complete Response (CR)	Disappearance of all TLs. Any pathological lymph nodes selected as TLs must have a reduction in short axis to <10mm.
Partial response (PR)	At least a 30% decrease in the sum of diameters of TLs, taking as reference the baseline sum of diameters as long as criteria for PD are not met.
Progressive disease (PD)	A ≥ 20% increase in the sum of diameters of TLs and an absolute increase of ≥ 5mm, taking as reference the smallest sum of diameters since treatment started including the baseline sum of diameters.
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD
Not Evaluable (NE)	Only relevant in certain situations (i.e. if any of the target lesions were not assessed or not evaluable or had a lesion intervention at this visit; and scaling up could not be performed for lesions with interventions). Note: If the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a target lesion response
Not applicable (NA)	No TLs are recorded at baseline

Rounding of TL data

For calculation of PD and PR for TLs percentage changes from baseline and previous minimum should be rounded to 1 d.p. before assigning a TL response. For example 19.95% should be rounded to 20.0% but 19.94% should be rounded to 19.9%

Missing TL data

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

Lymph nodes

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

TL visit responses subsequent to CR

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

1 Step 1: If all lesions meet the CR criteria (i.e. 0mm or < 10mm for lymph nodes) then response will be set to CR irrespective of whether the criteria for PD of TL is also met i.e. if a lymph node short axis increases by 20% but remains < 10mm.
2 Step 2: If some lesion measurements are missing but all other lesions meet the CR criteria (i.e. 0mm or < 10mm for lymph nodes) then response will be set to NE irrespective of whether the criteria for PD of TL is also met i.e. if a lymph node short axis increases by 20% but remains < 10mm.
3 Step 3: If not all lesions are missing, and those that are non-missing do not meet the CR criteria (i.e. a pathological lymph node selected as TL has short axis >= 10mm or the reappearance of previously disappeared lesion), then response will be set to PD.
4 Step 4: If all lesions are missing the response will be set to NE.

TL too big to measure

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

TL too small to measure

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

Irradiated lesions/lesion intervention

Previously irradiated lesions (i.e. lesion irradiated prior to entry into the study) should be recorded as NTLs and should not form part of the TL assessment.

Any TL (including lymph nodes), which has had intervention during the study (for example, irradiation / palliative surgery / embolization), should be handled in the following way and once a lesion has had intervention then it should be treated as having intervention for the remainder of the study noting that an intervention will most likely shrink the size of tumors:

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

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

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

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

Scaling

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

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

Example of scaling

Lesion 5 is missing at the follow-up visit; the nadir TL sum including lesions 1-5 was 74 mm.

The sum of lesions 1-4 at the follow-up is 68 mm. The sum of the corresponding lesions at nadir visit is 62 mm.

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

68 x 74 / 62 = 81 mm

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

Lesions that split in two

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

Lesions that merge

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

Change in method of assessment of TLs

CT, MRI and clinical examination are the only methods of assessment that can be used within a trial, with CT and MRI being the preferred methods and clinical examination only used in special cases. If a change in method of assessment occurs between CT and MRI this will be considered acceptable and no adjustment within the programming is needed.

If a change in method involves clinical examination (e.g. CT changes to clinical examination or vice versa), any affected lesions should be treated as missing. The TL visit response may still be evaluable if the number of missing TL measurements at a visit is ≤1/3 of the total number of TLs.

Non-Target Lesions (NTLs) and new lesions

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.

NTL response will be derived based on the Investigator's overall assessment of NTLs as described in Table 5.

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

Details of any new lesions will also be recorded with the date of assessment. The presence of one or more new lesions is assessed as progression.

A lesion identified at a follow up assessment in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

The finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor.

New lesions will be identified via a Yes/No tick box. The absence and presence of new lesions at each visit should be listed alongside the TL and NTL visit responses.

Table 5 NTL Visit Responses

Visit Responses	Description
Complete Response (CR)	Disappearance of all NTLs present at baseline with all lymph nodes non-pathological in size (<10 mm short axis).
Progressive Disease (PD)	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases, the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
Non-CR/Non-PD	Persistence of one or more NTLs with no evidence of progression.
Not Evaluable (NE)	Only relevant when one or some of the NTLs were not assessed and, in the investigator's opinion, they are not able to provide an evaluable overall NTL assessment at this visit. Note: For patients without TLs at baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met.
Not Applicable (NA)	Only relevant if there are no NTLs at baseline

A new lesion indicates progression so the overall visit response will be PD irrespective of the TL and NTL response.

If the question ‘Any new lesions since baseline’ has not been answered with Yes or No and the new lesion details are blank this is not evidence that no new lesions are present, but should not overtly affect the derivation.

Symptomatic progression is not a descriptor for progression of NTLs: it is a reason for stopping study therapy and will not be included in any assessment of NTLs.

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

Overall visit response

Table 6 defines how the previously defined TL and NTL visit responses will be combined with new lesion information to give an overall visit response.

Table 6 Overall visit responses

TARGET	NON-TARGET	NEW LESIONS	OVERALL VISIT RESPONSE
CR	CR or NA	No (or NE)	**CR**
CR	Non-CR/Non-PD or NE	No (or NE)	**PR**
PR	Non-PD or NE or NA	No (or NE)	**PR**
SD	Non-PD or NE or NA	No (or NE)	**SD**
PD	Any	Any	**PD**
Any	PD	Any	**PD**
Any	Any	Yes	**PD**
NE	Non-PD or NE or NA	No (or NE)	**NE**
NA	CR	No (or NE)	**CR**
NA	Non-CR/Non-PD	No (or NE)	**SD**
NA	NE	No (or NE)	**NE**
NA	NA	No (or NE)	**NED**

3.2.1.2 Objective response rate/Best objective response rate

Objective response rate

ORR is defined as the percentage of patients with a confirmed, programmatically determined CR or PR and will be based on a subset of all dosed patients evaluable for response with measurable disease at baseline per the site investigator.

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

responders in the ORR (i.e. both visits contributing to a response must be prior to subsequent therapy for the patient to be considered as a responder).

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

Best objective response

Best objective response (BoR) is calculated based on the overall visit responses from each RECIST assessment, described in Section 4.2.3.1. It is the best response a patient has had following first dose but prior to starting any subsequent cancer therapy and up to and including RECIST progression or the last evaluable assessment in the absence of RECIST progression. Categorisation of BoR will be based on RECIST using the following response categories: CR, PR, SD, PD and NE.

CR or PR must be confirmed. For determination of a best response of SD, the earliest of the dates contributing towards a particular overall visit assessment will be used. SD should be recorded at least 6 weeks minus 7 days, i.e. at least 35 days (to allow for an early assessment within the assessment window), after first dose/administration of study medication. For CR/PR, the initial overall visit assessment which showed a response will use the latest of the dates contributing towards a particular overall visit assessment.

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

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

For patients who die with no evaluable RECIST assessments, if the death occurs ≤ 79 days (i.e., 6 weeks + 8 weeks + 7 days to allow for a late assessment within the assessment window) after first dose/ administration of study medication, then BoR will be assigned to the progression (PD) category. For patients who die with no evaluable RECIST assessments, if the death occurs > 79 days after start of treatment then BoR will be assigned to the NE category.

A patient will be classified as a responder if the RECIST criteria for a confirmed CR or PR is satisfied at any time following first dose/administration of study medication, prior to RECIST progression or prior to starting any subsequent cancer therapy.

3.2.1.3 Change in tumor size

The best percentage change in tumour size from baseline will be reported, i.e. the maximum reduction from baseline or the minimum increase from baseline in the absence of a reduction from baseline based on all post baseline assessments:

- up to and including the first visit at which the overall visit response is PD,
- prior to death in the absence of progression,
- prior to the start of subsequent anti-cancer therapy (note: this should not include radiotherapy)
- or up to and including the last evaluable RECIST assessment if the participant has not died, progressed or started subsequent anti-cancer therapy.

Tumor size is the sum of the diameters of the target lesions. Target lesions are measurable tumor lesions. Baseline for RECIST is defined to be the last evaluable assessment prior to starting treatment, including the measurement occurring on the date of first dose/administration. The percentage change in target lesion tumor size at each visit for which data are available will be obtained for each patient taking the difference between the sum of the target lesions at each visit and the sum of the target lesions at baseline divided by the sum of the target lesions at baseline multiplied by 100 (i.e. (week x - baseline)/baseline * 100).

Only patients with measurable disease at baseline should be included in summaries of best percentage change in tumor size (measurable disease is as denoted on the CRF by the investigator).

If following the scaling up rules, best percentage change cannot be calculated due to missing data, and a patient has no post baseline assessments, then the following imputation rules should be applied:

1 If there is no observed TL tumor size measurement data post progression but there is evidence of progression for the individual during their time on study, where evidence of progression is defined as progression of NTLs, the appearance of new lesions or as determined by an investigator (i.e. investigator's opinion of response recorded on the RECIST CRF is PD at that assessment or study treatment was discontinued for progression in the assessment time window), and there are at least 5 patients with non-missing TL tumor size who have also progressed then impute a best percentage change from baseline as the median best percentage change from patients with non-missing TL tumor size who also have progressed. However if there are less than 5 patients with non-missing TL tumor size who have also progressed then impute a best percentage change from baseline as 20%.

2 If there is no evidence of progression, assume that the data is missing completely at random, the patient will be excluded from the analysis.

3 If it is known that the patient has died, impute a best percentage change from baseline as the maximum (i.e. corresponding to the biggest increase in TL tumor size) best percentage change reported on the study.

3.2.2 PSA response rate

PSA response rate is defined as the proportion of patients achieving a ≥50% decline from baseline to the lowest post-baseline PSA results, confirmed by a second consecutive PSA assessment at least 3 weeks later. Ignore early rises (before 12 weeks) in determining PSA response

- A patient will be regarded as having a single PSA visit response if their PSA level at any post-dose visit is reduced by 50% or more compared with baseline
- A patient will be regarded as having a confirmed PSA response if they have a reduction in PSA level of 50% or more compared with baseline that is confirmed at the next assessment at least 3 weeks later (i.e., decrease relative to baseline of at least 50% documented on 2 consecutive occasions at least 3 weeks apart).

PSA progression

If there is a PSA decline from baseline, progression is defined as the date of the first PSA increase that is both ≥25% and ≥2 ng/mL above the nadir and which is confirmed by a second value ≥3 weeks later, even if within 12 weeks.

If there is no PSA decline from baseline, progression is defined as a ≥25% increase and ≥2 ng/mL increase from baseline beyond 12 weeks.

The proportion of patients achieving a PSA response and patients with a confirmed PSA response will be presented with both 95% CI and 80% CI. The best PSA percentage change from baseline and the percent change from baseline in PSA levels at 12 weeks will be summarized and graphed. Waterfall plots (bar plots), and spider plots (individual line plots of percent change from baseline over time) will be produced.

3.3 Secondary outcome variables

3.3.1 Duration of response (DOR)

Duration of response will be defined as the time from the date of first documented response (which is subsequently confirmed) until date of documented progression or death in the absence of disease progression (ie, date of PFS event or censoring – date of first response + 1). The end of response should coincide with the date of progression or death from any cause

used for the PFS endpoint. The time of the initial response will be defined as the latest of the dates contributing towards the first visit that was PR or CR that was subsequently confirmed.

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

3.3.2 Radiological Progression-Free Survival (rPFS)

rPFS is defined as the time from first dose of AZD4635 until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from study therapy or receives another anti-cancer therapy prior to progression (i.e. date of event or censoring – date of first dose + 1).

Patients who have not progressed (defined as CR, PR or SD by RECIST v1.1 for soft tissue disease, or non-PD for bone disease) or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST assessment or bone scan. However, if the patient progresses or dies after two or more missed radiologic visits, the patient will be censored at the time of the latest evaluable RECIST 1.1 or bone scan assessment prior to the two missed visits. Given the scheduled visit assessment scheme (i.e. six-weekly for the first 6 weeks and then eight-weekly thereafter) the definition of 2 missed visits will change.

1 If the two missed visits occur over the period when the scheduled frequency of assessments changes from six-weekly to eight-weekly this will equate to 15 weeks or 105 days (i.e. take the average of 6 and 8 weeks which gives 7 weeks and then 2 x 7 weeks + 1 week for a late assessment = 15 weeks). The time period for the previous assessment will be until study day 35 (i.e. up to week 5).
2 If the previous assessment is from week 5 (day 36) onwards (when the scheduling changes to eight weekly assessments), two missing visits will equate to 18 weeks or 126 days (i.e. 2 x 8 weeks + 1 week for an early assessment + 1 week for a late assessment = 18 weeks).

Progression-free follow-up are scheduled every 3 months (±1 week) for those patients without objective PD at the time of the study drug discontinuation. 3 months is approximately 13 weeks.

1 If the two missed visits occur over the period when the scheduled frequency of assessments changes from eight-weekly to 3-monthly this will equate to 23 weeks or 161 days (i.e. take the average of 8 and 13 weeks which gives 10.5 weeks and then 2 x 10.5 weeks + 1 week for an early assessment + 1 week for a late assessment = 23 weeks).

2 If the two missing visits occur when the scheduling changes to 3-monthly assessment, two missing visits will equate to 28 weeks or 196 days (i.e. 2 x 13 weeks + 1 week for an early assessment + 1 week for a late assessment = 28 weeks).

If a patient has an assessment for soft tissue disease (MRI/CT) but not for bone disease (bone scan), or vice versa, then this will count as a missed assessment.

If the patient has no evaluable post-baseline RECIST v1.1 or bone scan assessment, they will be censored at 1 day unless they die within 2 visits of baseline (in which case their date of death will be used).

The PFS time will always be derived based on scan/assessment dates not visit dates. RECIST assessments/bone scans contributing towards a particular visit may be performed on different dates. The following rules will be applied:

1 For investigational assessments, the date of progression will be determined based on the **earliest** of the dates of the component that triggered the progression
2 When censoring a patient for PFS the patient will be censored at the **latest** of the dates contributing to a particular overall visit assessment.

3.3.3 Overall survival (OS)

Overall survival is defined as the time from the date of first dose until death due to any cause regardless of whether the patient withdraws from study therapy or receives another anti-cancer therapy (i.e. date of death or censoring – date of first dose + 1). Any patient not known to have died at the time of analysis will be censored according to the following rules.

1 If the patient is lost to follow-up immediately after 1st dose of study drug, the patient will be censored at the date of 1st dose of study drug.
2 If the patient is not known to have died at or after the analysis cutoff date, the patient will be censored at the date last known alive before data analysis cutoff.
3 If the patient is known to have died after the analysis cutoff date, the patient will be censored at the date of analysis cutoff.

Note: Survival calls will be made in the week following the date of data cut-off (DCO) for the analysis, and if patients are confirmed to be alive or if the death date is post the DCO date these patients will be censored at the date of DCO. The status of ongoing, withdrawn (from the study) and “lost to follow-up” patients at the time of the final OS analysis should be obtained by the site personnel by checking the patient’s notes, hospital records, contacting the patient’s general practitioner and checking publicly-available death registries. In the event that the patient has actively withdrawn consent to the processing of their personal data, the vital

status of the patient can be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws.

Note that for any OS analysis performed prior to the final OS analysis, in the absence of survival calls being made, it may be necessary to use all relevant CRF fields to determine the last recorded date on which the patient was known to be alive for those patients still on treatment. The last date for each individual patient is defined as the latest among the following dates recorded on the case report forms (CRFs):

1 AE start and stop dates
2 Admission and discharge dates of hospitalization
3 Study treatment date
4 End of treatment date
5 Laboratory test dates
6 Date of vital signs
7 Disease assessment dates
8 Start and stop dates of alternative anticancer treatment
9 Date last known alive on survival status CRF
10 End of study date

3.3.4 Calculation or derivation of pharmacokinetic variables

Pharmacokinetic samples for steady state trough of the plasma concentration for AZD4635 and serum concentration for durvalumab and oleclumab will be summarized in the CSR. No parameters will be calculated. CCI [redacted]

3.3.5 CCI [redacted]

CCI [redacted]

3.4 Safety outcome variables

3.4.1 Duration of exposure

Duration of exposure is defined as:

1 Total treatment duration of AZD4635 (in months) = min((last dose date where dose > 0 [units], date of death, date of DCO) – first dose date +1) / (365.25/12)

Total treatment duration of durvalumab = min ((last dose date where dose > 0 +27, date of death, date of DCO) − date of first dose +1) / (365.25/12)

Total treatment duration of oleclumab = min ((last dose date where dose > 0 +***27***, date of death, date of DCO) − date of first dose +1) / (365.25/12)

***** it should be noted that for cycle 0, 13 should be added, instead of 27. This only applies to oleclumab.*

2 Actual treatment duration of AZD4635 = total treatment duration – total duration of dose interruptions, where total treatment duration will be calculated as above and a dose interruption is defined as any length of time where the patient has not taken any of the planned daily dose.

3 Duration of therapy at starting dose = actual treatment duration for the dose assigned.

It should be noted that a snapshot date might be used instead of the date of DCO, as applicable.
The actual treatment duration calculation makes no adjustment for any dose reductions that may have occurred.

Exposure will also be measured by the number of cycles received for IV administered treatment (durvalumab and oleclumab). A cycle corresponds to a period of 14 days for Cycle 0 (oleclumab) and 28 days for Cycle 1 and beyond. If the last dose is in Cycle 0, the number of cycles received will be 1. If a cycle is prolonged due to toxicity, this should still be counted as one cycle. A cycle will be counted if treatment is started even if the full dose is not delivered.

For handling exposure and dose interruptions, the following rules will be considered.

Missed or forgotten doses

Missed and forgotten doses should be recorded on the TREATMENT – AZD4635/ TREATMENT – Oleclumab/ TREATMENT - Durvalumab module as ‘drug interrupted’. These missed or forgotten doses will not be included as dose interruptions in the summary tables but the information will appear in the listing for dosing. However, these missed and forgotten doses will be considered in the derivation of actual exposure.

Patients who permanently discontinue during a dose interruption

If a patient permanently discontinues study treatment during a dose interruption, then the date of last administration of study medication and other assessment data recorded on END OF

TREATMENT – AZD4635/ END OF TREATMENT – Oleclumab/ END OF TREATMENT/ Durvalumb (as applicable), will be used in the programming.

3.4.2 Dose intensity

Dose intensity of each individual therapy will be addressed by considering relative dose intensity (RDI), and will be derived as detailed below.

- Relative dose intensity (RDI) is the percentage of the actual dose delivered relative to the intended dose through to treatment discontinuation. The RDI is equal to 100% * d/D, where d is the actual cumulative dose delivered up to the earlier of progression (or a censoring event) or actual last day of dosing, and D is the intended cumulative dose up to the earlier of progression (or a censoring event) or the actual last day of dosing plus the protocol-defined post-dose rest period.

It should be noted for Module 2 that the initial patients received a dose of AZD4635 50 mg PO QD and oleclumab 1500 mg Q2W for the first 4 doses and Q4W thereafter. Following the SRC meeting and the protocol amendment being implemented at sites, subsequent patients began treatment at the AZD4635 75 mg dose, and continued with that dose.

3.4.3 Adverse events

AEs and SAEs will be collected throughout the study, from date of informed consent until 30 days after the end of the last investigational product administration (90 days for the durvalumab and oleclumab) . Events will be defined as treatment emergent if they begin, or worsen (by investigator report of a change in intensity), during the treatment period, i.e., starting after the first dose of therapy or within 30 days after the end of the last investigational product (90 days for the durvalumab and oleclumab; see further details in section 4.2.5.2). The Medical Dictionary for Regulatory Activities (MedDRA) (version 21.1 or higher) will be used to code the AEs. AEs will be graded according to the National Cancer Institute Common Terminology Criteria for AEs (CTCAE Version 5.0).

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the IP and may require close monitoring and rapid communication by the investigator to the sponsor. More information regarding AESIs can be found in the module specific appendices to the clinical study protocol. Other categories may be added or existing terms may be modified as necessary. Further reviews may take place prior to database lock (DBL) to ensure any further terms not already included are captured within the categories. Preferred terms used to identify AESI will be listed before DBL.

Immune Mediated Adverse Events (imAE) are defined as a subset of AESI that consider interventions of corticosteroids, immunosuppressants, and/or endocrine therapy; are deemed consistent with having an immune-mediated mechanism of action and where there was no

clear alternative etiology. Automated adjudication approach via programming will be used to identify the imAEs, and will be reported outside of the CSR.

Other significant adverse events (OAE)

During the evaluation of the AE data, Medical Monitor will review the list of AEs that were not reported as SAEs and AEs leading to discontinuation of investigational product. Based on the expert's judgement, adverse events of particular clinical importance may, after consultation with the Medical Science Director, be considered other significant adverse events (OAEs) and reported as such in the Clinical Study Report. A similar review of laboratory values, vital signs, ECGs and other safety assessments will be performed for identification of other significant adverse events. This review will take place prior to database lock, and any AEs identified will be fully documented in meeting minutes. Further review following database lock may result in ad-hoc OAEs being identified, in this case, the OAEs and resulting summaries will be fully documented in the CSR.

3.4.4 ECG changes

ECG will be obtained at screening, end of treatment and when clinically indicated. QTc intervals will be collected in msec. For numeric ECG parameters, change from baseline in ECG variables will be calculated for each post-dose visit (if available) on treatment, and at the end of treatment. . It should be noted that the ECGs are to be performed in triplicates. As such, the ECG parameters shall be averaged and then summarized, as applicable .

3.4.5 Echocardiography or muli-gated acquisition scan (ECHO/ MUGA)

Echocardiogram or multi-gated acquisition scan will be performed at screening and within 14 days after a clinically significant ECG finding. ECHO/ MUGA may also be repeated at the end of treatment visit to address recovery during off-treatment period.

3.4.6 Vital sign changes

Change from baseline in vital signs variables will be calculated for each post-dose visit on treatment. Vital signs including blood pressure (BP), pulse, respiration, temperature and weight will be collected at module specific timepoints. Blood Pressure and pulse will be collected before, during and after the first infusion visit, including 2 or more readings of BP pre-infusion. For the subsequent visits, all vital signs will be recorded prior to start of infusion and also during, post infusion as per institutional standard and as clinically indicated.

3.4.7 Laboratory data

Change from baseline in haematology, clinical chemistry and urinalysis variables will be calculated for each post-dose visit on treatment. CTCAE (version 5.0) grade will be

calculated at each visit. Maximum post-baseline CTC will also be calculated. Absolute values will be compared to local laboratory reference ranges and classified as low (below range), normal (within range or on limits of range) and high (above range). All values classified as high or low will be flagged on the listings.

3.4.8 Creatinine clearance

Estimated creatinine clearance will be calculated using the Cockcroft and Gault formula as follows:

$$\frac{(140 - \text{age [years]}) \times \text{weight [kg]} \times 1.23}{\text{creatinine [}\mu\text{mol/L]}}$$

4 ANALYSIS METHODS

4.1 General principles

The local laboratory reference ranges will be used for laboratory data. The below mentioned general principles will be followed throughout the study:

- Descriptive statistics will be used for all variables, as appropriate. Continuous variables will be summarized by the number of observations, mean, standard deviation, median, minimum, and maximum. For log-transformed data, it is more appropriate to present geometric mean, geometric standard deviation, coefficient of variation (CV), median, minimum and maximum. Categorical variables will be summarized by frequency counts and percentages for each category.
- If data are available for less than 3 patients, no summary statistics other than minimum, maximum and number of observations will be presented.
- Unless otherwise stated, percentages will be calculated out of the analysis set total and for each module.
- For continuous data, the mean and median will be rounded to 1 additional decimal place compared to the original data. The standard deviation will be rounded to 2 additional decimal places compared to the original data. Minimum and maximum will be displayed with the same accuracy as the original data.
- For categorical data, percentages will be rounded to 1 decimal place.
- For PK data, various significant figures will be used as standard.
- SAS Institute 2001® version 9.4 or higher will be used for all analyses.
- It is acceptable to present large numerical values in more appropriate units. For example, an AUC value of 123,000 ng·h/mL may be reported as 123 µg·h/mL instead of 123,000 ng·h/mL. It is, however, important to keep the units consistent within the report and the precision consistent with that prior to conversion.

4.2 Analysis methods

Summaries will be presented separately by module. There is no formal statistical analysis required for this study.

4.2.1 Randomization

Randomization will occur when patients meet eligibility criteria for 2 or more modules that are currently recruiting. If patients only meet the criteria for 1 currently recruiting module, they will be allocated to that module without randomization taking place. All patients allocated or randomized will be stratified by patients with either bone only metastasis or measurable soft tissue metastasis to ensure there is sufficient number of patients in each group as specified in the module sample size.

4.2.2 Disposition, demography, and baseline characteristics

Disposition, demography, baseline characteristics (including disease characteristics), protocol deviations, concomitant medications and medical history will be listed and summarized by module. Any study disruptions due to COVID-19 pandemic will be summarized by module.

4.2.2.1 Patient disposition

The reasons for each study treatment discontinuation and study discontinuation will be summarized with the number and percentage of patients. This will include patients who discontinued treatment due to the pandemic and who withdrew from study due to the pandemic. Percentages are calculated from number of patients who received treatment in each module.

- Enrolled
- Treated
- Ongoing treatment
- Discontinued treatment
- Reasons for treatment discontinuation (including the reason due to COVID-19 pandemic)
- Ongoing study
- Discontinued study
- Reasons for study discontinuation (including the reason due to COVID-19 pandemic)

4.2.2.2 Analysis sets

- Enrolled
- Safety
- DLT (Module 2)
- Pharmacokinetics (PK)
- Tumor response

- Evaluable for Efficacy
- PSA Reponse

4.2.2.3 Protocol deviations

The number and percentage of patients with important protocol deviations in each deviation category will be summarized, including number and percentage of participants with at least one important protocol deviation related to the pandemic. Important protocol deviations will be listed. Patients affected by the COVID-19 pandemic will be listed including category for study disruption due to the pandemic and details of the disruption. The examples of the categories are shown in Section 2.2.

4.2.2.4 Demography and baseline characteristics

The non-missing numerical values will be summarized as mean, median, standard deviation, minimum and maximum; while the categorical values will be summarized as frequency and percentage.

- Demographic characteristics include age, sex, race, ethnicity, and age group (<50, ≥ 50 - < 65, ≥ 65 - < 75 and ≥ 75 years)
- Baseline characteristics include height, weight, weight group (< 70, 70 to 90, > 90), BMI and BMI group (Normal (< 25), Overweight (25-30), Obese (>30)).

4.2.2.5 Disease diagnosis and staging

The number and percentage of patients with the corresponding categorical values in disease diagnosis and staging will be summarized including:

- Eastern Cooperative Oncology Group (ECOG) performance status
- Primary Diagnosis
- Histology and histological grade
- Stage: TNM stage at diagnosis, stage classification
- Gleason Score
- Metastatic site at study entry
- No of metastatic sites at study entry
- Time from diagnosis to enrolment

For the missing diagnostic dates, if day and/ or month are missing, use 01 and/ or Jan. IF year is missing, put the complete date to missing.

4.2.2.6 Prior therapies

The number and percentage of patients with prior systemic therapy, prior radiation, and prior surgery will be summarized by category (e.g. chemotherapy, radiotherapy, etc.) and the number of regimens.

- Number of each therapy type (0, 1, 2, 3, 4, 5, 6, >6)
- Percentage of patients receiving one or more courses of prior therapy by type.
- Best overall response, if applicable
- Summary of prior systemic therapy drugs by WHO preferred name and disease setting
- Summary of prior surgery by MedDRA system organ class and preferred term

4.2.2.7 Concomitant medications

World Health Organization (WHO) Drug Dictionary March 2016 will be used for coding medication terms.

- Prior medications are those taken prior to study treatment with a stop date prior to the first dose of study treatment.
- Concomitant medications are those with a stop date on or after the first dose date of study treatment (and could have started prior to or during treatment).
- Post-treatment medications are those with a start date after the last dose date of study treatment.

Imputed dates are not to be used to calculate durations.

Concomitant medications will be summarized (frequency and percentage of patients) by WHO drug preferred name. Each unique drug will be counted once per patient. The summary will be ordered by decreasing total frequency of use. Disallowed concomitant medications will be summarized and listed.

Appendix J of the Core Clinical Study Protocol lists the disallowed medications for AZD4635. Details for other study treatments are provided in the modular-specific appendix. A separate summary of any disallowed concomitant medications taken by a patient will be tabulated.

4.2.2.8 Medical History

Medical will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 21.1 or higher. The frequency and percentage of patients with each condition will be summarized by System Organ Class (SOC) and preferred term (PT). Patients with multiple unique terms will be counted once per each unique PT and unique SOC. Each summary will be ordered by decreases frequency of PT within SOC. A listing of medical history will be provided as well.

4.2.3 Tumor response and efficacy

Objective response rate (ORR) will be summarized for dosed patients with measurable disease at baseline. BOR will be summarized for dosed patients with measurable disease at baseline and separately for dosed patients evaluable for efficacy.

Tumor response data will be summarized by module, if appropriate, using the following response categories: CR, PR, SD, PD, and not evaluable (NE).

Details of tumor assessment and response will be listed for each patient. This listing will include information on lesion site, the method of assessment, diameter of lesion, sum of diameters of lesions, percent change from baseline, the calculated visit response, non-target lesions, new lesions, best objective response.

4.2.3.1 Best objective response and Objective response rate

The proportion of patients achieving an objective response (CR or PR) will be presented with a two-sided 95% CI, as well as 80% CI,using the Clopper-Pearson method (Clopper and Pearson 1934). The Objective response rate (ORR) will be presented separately for each module. The number and percentage of patients in each RECIST response category (CR, PR, SD, PD, and NE) will be summarized for each module.

4.2.3.2 Change in tumor size

Target lesion size at each tumor assessment time point will be summarized, along with percentage change from baseline.imputation will not be used for the calculation of percent change in tumor size)Also, the best percentage change in tumor size from baseline over all tumor assessment time points will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum).

Waterfall plots indicating the best percentage change from baseline in sum of the diameters of target lesions will be produced. The plot will present each patient's best percentage change from baseline in TL tumor size as a separate bar, with the bars ordered from the largest increase to the largest decrease. A reference line at the –30% change in TL tumor size level will be added to the plots, which corresponds with the definition of 'partial' response. Best overall response will be color coded. The scale in these plots will be fixed to be from -100 to 100 to avoid presenting extreme values. Values that are capped as a result of this restriction to the scale are marked with '#'. Values will be ordered in descending order with the imputations due to death appearing first followed by a gap followed by all other patients. Imputed values will be clearly marked with '*' and patients with imputation where there was a death or evidence of progression have different shading to each other and the other patients to make it clear that these are different.

Additionally, 'spider' plots (individual line plots of percent change from baseline over time) indicating the percentage change from baseline in sum of the diameters of TLs will be produced by dose level. This depicts each patient's percentage change in TL tumor size as a line over time and progression due to non- target and/or new lesions will be indicated. (Imputation will not be used for spider plots.)

4.2.3.3 Radiological Progression-free survival

Summaries (number of events, medians, proportion and 95% confidence interval for progression free at 3, 6, 9 months and 12 months using the Kaplan-Meier estimate) and Kaplan Meier plots will be provided. A 2-sided 95% confidence interval for the median PFS will be produced in addition to the 25th and 75th percentiles. A listing of progression details will be provided.

4.2.3.4 Duration of response

Duration of Response will be analysed in the same manner as PFS, if patient numbers allow. A swimmer plot will be presented with the duration of response over time. The bars in the swimmer plots indicate the duration of response for each subject, the y-axis will indicate the subject ID.

4.2.3.5 Overall survival

4.2.3.6 Overall Survival will be analyzed in the same manner as PFS if patient numbers allow. CCI

CCI [redacted]

4.2.4 PSA response

The proportion of patients achieving a PSA response and patients with a confirmed PSA response will be presented with both 95% CI and 80% CI. The best PSA percentage change from baseline and the percent change from baseline in PSA levels at 12 weeks will be summarized and graphed. For patients who receive a subsequent anti-cancer therapy (note that for this analysis radiotherapy is not considered a subsequent anti-cancer therapy), data will only be included until the start date of the subsequent anti-cancer therapy.

Waterfall plots (bar plots) for the best percent change from baseline in PSA levels will be presented with each bar corresponding to the best percent change from baseline in PSA level for each patient, with the bars ordered from the largest increase to the largest decrease. The scale in these plots will be fixed to be from -100 to 100 to avoid presenting extreme values. Values that are capped as a result of this restriction to the scale are marked with '#'.

Additionally spider plots (individual line plots of percent change from baseline over time) depicting the percent change from baseline in PSA levels, at different dose levels over time, for each patient will be produced.

4.2.5 Safety analyses

Safety data will not be formally analyzed. At the end of the study, appropriate summaries for all safety data will be produced, as defined below. All patients who received at least 1 dose of study drug will be included in the assessment of the safety profile (safety analysis set).

4.2.5.1 Exposure

Exposure to investigational product i.e., total amount of study drug received, will be listed for all patients.

Reasons for discontinuation of investigational product will be listed including the study day of treatment discontinuation and will be summarized by dose level if appropriate.

Total exposure, number of infusion cycles (where applicable), total treatment duration (as defined in Section 3.4.1), and the amount delivered relative to the intended amount (dose intensity: RDI) will be summarized by the following: mean, standard deviation, minimum, maximum, median and number of observations. In addition, the number and percentage of patients with at least one dose interruption and at least one dose reduction will be presented separately for the initial period of DLT evaluability (Module 2 only) and for total treatment duration.

A swimmer plot will be produced for duration of exposure of study treatment. For each patient (indicated on the Y-axis) , the corresponding bar represents over time - the best response (CR, PR, SD, PD, NE) or no measurable disease, the beginning of RECIST and PSA response, time of RECIST and/or PSA progression, and whether the treatment is still ongoing or not.

4.2.5.2 Adverse events/ Serious adverse events

Adverse events (including laboratory-related adverse events) will be coded with System Organ Class (SOC) and Preferred Term (PT) using MedDRA version 21.1 or higher.

Adverse events occurring on (could be on the same day as the first dose of IP, but at an earlier time) or before the first dose of IP (pre-treatment adverse events) or >30 days post the last dose i.e within 30 days after the end of the last investigational product (90 days for durvalumab and oleclumab) will be listed separately. For module 1, adverse events onsetting or worsening on/after the first dose of study treatment up until the defined 30 day follow up period following end of AZD4635 or 90 days following end of durvalumab – whichever is later; and for module 2, adverse events onsetting or worsening on/after the first dose of study treatment up until 90 days following end of treatment will be summarized by MedDRA

system organ class (SOC) and MedDRA preferred term (PT), with further splits by maximum CTCAE grade, possibly related to study medication as assessed by investigator, dose interruption or modification, and adverse events classed as CTCAE Grade 3 or higher. Additional tables will summarize AEs with outcome of death.

Generally, the imputation of dates is used to decide if an observation is treatment emergent for adverse events or concomitant medications. The imputed dates are not advised to be used to calculate durations where the results would be less accurate. After querying, dates will be imputed as described in the "Missing dates" part in section 3.1 of this SAP.

Flags will be retained in the database indicating where any programmatic imputation has been applied, and in such cases, any durations would not be calculated.

Separate tables will present adverse events leading to discontinuation, serious adverse events and other significant adverse events. All AE data will be listed appropriately.

Cause of death will be summarized and the details of any deaths will be listed for all patients.

In addition, adverse events of special interest will be summarized in a similar manner as TEAEs. The listing of preferred terms and categories will be provided by AZ patient safety lead based on Medical Review at end of study, prior to database lock (DBL).

For Module 2, a DLT table will be generated showing the number of patients experiencing a DLT together with the total number of DLTs by patient. This table will use the DLT Analysis set.

4.2.5.3 Laboratory results

Clinical laboratory assessments for this study include: haematology, clinical chemistry, coagulation, and urinalysis.

Haematology, clinical chemistry, and coagulation parameters will be summarized as follows:

- Change and percentage change from baseline by module and visit (including mean, median, standard deviation, maximum, and minimum) (unscheduled assessments will not be included)
- Shift from baseline to maximum post-baseline CTCAE grade (unscheduled assessments will be included) if applicable

.For urinalysis, the number and percentage of patients shifting from baseline to maximum abnormal results through treatment discontinuation will also be summarized . For electrolytes, CTCAE grade change from baseline to maximum on treatment high and low will be summarized.

4.2.5.4 Monitoring for drug-induced liver injury

The patients who had ALT ≥3xULN or AST ≥3xULN together with total bilirubin ≥2xULN will be listed for the safety analysis set. The listing will include absolute values along with a function of the upper limit of normal (ULN) ALT, AST, total bilirubin and ALP. Any potential Hy's law case will be listed.

4.2.5.5 Electrocardiographic (ECG)

The ECG parameters will be summarized numerically and categorically for the safety analysis set

- Change and percentage change of ECG parameters from baseline by visit and module (including mean, median, standard deviation, maximum, and minimum)
- The number and percentage of patients with maximum on-treatment QTcF values >450, >480, >500 msec by module
- The number and percentage of patients with the QTcF maximum changes as >30, >60, >90 msec by module.

ECG data will also be listed.

4.2.5.6 Echocardiography or Multi-gated acquisition scan (ECHO/ MUGA)

All available data for ECHO/ MUGA, if performed to assess the ejection fraction, will be listed.

4.2.5.7 Vital signs assessments

Vital signs (e.g. weight, heart rate, respiratory rate, systolic blood pressure, diastolic blood pressure, and body temperature) will be summarized and listed for the safety analysis set. As per the protocol specified requirements, the baseline vital signs parameters of systolic and diastolic blood pressure were recorded 2 or more times. These values will be averaged and summarized. Result and percentage change from baseline by visit and module (including mean, median, standard deviation, maximum, and minimum). On the day of the first infusion, the vital signs were collected pre, during, and post infusion, and this will be reflected in the summary,

- From baseline at each visit through treatment discontinuation

4.2.6 Pharmacokinetics data

PK concentrations of AZD4635, Durvalumab and Oleclumab will be analyzed descriptively by summarizing data at each scheduled time point (pre-dose and/or post dose) based on observed data. Additionally, the PK concentrations will be presented in box plots separately,

one each for AZD4635, Durvalumab and Oleclumab. PK concentrations not assigned to a scheduled time point will be listed only. Plasma/serum concentrations below the lower limit of quantification (LLOQ) will be reported as not quantifiable (NQ) with LLOQ defined in the TFLs.

CCI [redacted]

CCI [redacted]

Plasma concentrations will be summarized by module, cycle, day and nominal sample time. Plasma concentrations of AZD4635 and its metabolites will be summarized by nominal sample time. Parameters concentrations will be summarized by the following summary statistics:

- The geometric mean (gmean, calculated as exp [μ], where μ is the mean of the data on a logarithmic scale)
- Coefficient of variation (CV, calculated as 100 √ [exp(s2)-1], where s is the standard deviation of the data on a loge scale)
- Gmean + geo standard deviation(geoSD) (calculated as exp[μ +s])
- Gmean – geo standard deviation (geoSD) (calculated as exp[μ-s])
- Arithmetic mean calculated using untransformed data
- Standard deviation calculated using untransformed data
- Median
- Minimum
- Maximum
- Number of observations
- Number of observations above the lower limit of quantification (LLOQ)

Handling of non-quantifiable plasma concentrations (at a given time point)

Non-quantifiable (NQ) values of plasma concentrations (at a given time point) will be handled as follows:

- For timepoints prior to first measurable concentration, substitute 0.
- If 50% or less of the values are NQ, the gmean, CV, gmean + geo standard deviation, gmean – geo standard deviation, arithmetic mean and standard deviation will be calculated by substituting the limit of quantification (LOQ) for values which are NQ.
- If more than 50%, but not all, of the values are NQ, the gmean, CV, gmean + standard deviation, gmean - standard deviation, arithmetic mean and standard deviation will be

reported as not calculable (NC). The maximum value will be reported from the individual data, and the minimum and median will be set to NQ.

- If all the values are NQ, no summary statistics will be calculated. The gmean, arithmetic mean, minimum, median, and maximum will be reported as NQ. The CV, gmean + standard deviation, gmean - standard deviation, and standard deviation will be set to NC.

At least 3 observations are required for concentrations to be summarized. If data are available for less than 3 observations, no summary statistics other than minimum, maximum and n will be presented.

For any gmean plasma concentration-time plots where a gmean was unable to be calculated as there were fewer than 3 patients for that dose group, the individual patient profile(s) for that dose group could be included instead of the gmean.

4.2.7 Immunogenicity

CCI [redacted]

Presence of ADAs to study drug(s) in combination with AZD4635 (confirmatory results: positive or negative) will be listed for each time point, and included in the CSR.

4.2.8 Exploratory research variables

CCI [redacted]

5 INTERIM ANALYSES

No formal interim analysis is planned.

6 CHANGES OF ANALYSIS FROM PROTOCOL

There are no changes of analysis from the protocol.

7 REFERENCES

Clopper and Pearson 1934
Clopper, C. and Pearson, E. S. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 26: 404-413, 1934

SAS Institute 2001
SAS Institute Inc. (2001): The SAS System, Version 8.2. Cary, NC. SAS Institute Inc.

CCI [redacted]

SIGNATURE PAGE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature

Document Name: d8731c00001-sap-ed-2		
Document Title:	Statistical Analysis Plan Edition 2	
Document ID:	CCI [redacted]	
Version Label:	2.0 CURRENT LATEST APPROVED	
Server Date **(dd-MMM-yyyy HH:mm 'UTC'Z)**	**Signed by**	**Meaning of Signature**
12-Nov-2021 08:36 UTC	PPD	Qualified Person Approval

CCI [redacted]