A Phase I/IIa, Open-Label Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Efficacy of Ascending Doses of AZD7648 Monotherapy or in Combination with either Cytotoxic Chemotherapies or Novel Anti-Cancer Agents in Patients with Advanced Malignancies

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AstraZeneca

Statistical Analysis Plan

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A Phase I/IIa, Open-Label Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Efficacy of Ascending Doses of AZD7648 Monotherapy or in Combination with either Cytotoxic Chemotherapies or Novel Anti-Cancer Agents in Patients with Advanced Malignancies

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LIST OF ABBREVIATIONS

Abbreviation or special term*	Explanation
AE	Adverse event
Ae(t1-t2)	Amount of drug excreted unchanged into urine from time t1 to t2.
AUC	Area under the plasma concentration time curve
AUCinf	Area under the plasma concentration time curve from time zero to infinity.
AUCτ	Area under the plasma concentration time curve in the dose interval
AUC(0-12)	Area under the plasma concentration-time curve from time zero to 12 hours post-dose.
AUC(0-24)	Area under the plasma concentration-time curve from time zero to 24 hours post-dose.
AUClast	Area under the plasma concentration-time curve from time zero to last quantifiable concentration.
AUCextr	Extrapolated area under the curve from tlast to infinity, expressed as percentage of AUCinf
BoR	best objective response
Cavg	Average drug concentration over a dosing interval
CI	confidence interval
Cmax	Maximum observed plasma (peak) drug concentration
Ctrough	Lowest observed plasma (trough) drug concentration reached before the next dose is administered.
CL/F	Apparent total body clearance of drug from plasma after extrvascular administration.
CLR	Renal clearance of drug from plasma
CR	Complete response
CrCL	Creatinine clearance
CSP	Clinical study protocol
CSR	Clinical study report
CCI	CCI
CTCAE	Common Terminology Criteria for Adverse Event
CCI	CCI
CV	Coefficient of variation

Abbreviation or special term*	Explanation
DCO	Data cut-off
DLT	Dose-limiting toxicity
DoR	Duration of response
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
fe(t1-t2)	Percentage of dose excreted unchanged in urine from time t1 to time t2
GI	Gastrointestinal
GPS	Global product statistician
gSD	Geometric standard deviation
h	Hour
HR	Homologous recombination
HRR*m*	Homologous recombination repair *mutation*
IPD	Important protocol deviations
MedDRA	Medical Dictionary for Regulatory Activities
MRTinf	Mean residence time of the unchanged drug in the systemic circulation
NA	Not applicable
NC	Not Calculated
NE	Not evaluable
NPD	Non progressive disease
NTL	Non target lesion
NQ	Not quantifiable
OS	Overall surivival
PD	Progressive disease
PDc	Pharmacodynamic
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PLD	Pegylated liposomal doxorubicin
PR	Partial response

Abbreviation or special term*	Explanation
QTc	Corrected QT interval
Rac	Accumulation ratio
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumours
Rsq adj	Statistical measure of fit for the regression used for λz determination adjusted for the number of used data points (λzN)
SAP	Statistical analysis plan
SD	Stable disease in RECIST assessments / Standard deviation in statistical summaries
t	Time
TCP	Temporal change parameter in systemic exposure
TL	Target lesion
t½λz	Half-life associated with terminal slope (λz) of a semi-logarithmic concentration-time curve
tlast	Time of last observed (quantifiable) concentration
tmax	Time to reach peak or maximum observed concentration or response following drug administration
tsm	Tumour size measurement
ULN	Upper limit normal
Vss/F	Volume of distribution (apparent) at steady state following extravascular administration
Vz/F	Volume of distribution (apparent) following extravascular administration (based on terminal phase)
τ	Dose interval (tau)
λz	Terminal elimination rate constant
λz lower	Lower (earlier) t used for λz determination
λz upper	Upper (later) t used for λz determination
λzN	Number of data points used for λz determination
λz span ratio	Time period over which λz was determined as ratio of t½λz

*The PK abbreviations and definitions are updated from those in the CSP in line with current AZ guidance for PK reporting

VERSION HISTORY

Version 1.0, 16 September 2019

New document.

Version 2.0, 25 June 2021

Section 1.0

A new section 1.1 added with brief introduction to the study and the list of documents on which this statistical analysis plan is based.

A new section 1.2 added to list out available modules of the study as per latest protocol amendment.

Within Table 1 Corrected the spelling 'pharamcodynamic' to 'pharmacodynamic'

Added that AUC_{0-t} and C_{max} ratio for food effect is only applicable to food effect cohort in the monotherapy expansion phase.

Added that Post-dose to pre-dose 4β-hydroxy cholesterol ratio is only applicable to monotherapy cohorts.

A footnote a is added.

Section 2.1 New section added.

A paragraph added to briefly explain how the data will be analysed and CSR will be created for each module and part.

Previous section 2.1 Analysis set was re-numbered as 2.2

The paragraph has been modified to be specific how the efficacy analysis sets are classified:

according to module, part, cohort or planned dose

Within Table 2 Deleted duplicate entry for *Best Objective response* in the efficacy data.

Restructured the sentence under endpoint 'Pharmacodynamics' as follows.

A new analysis set ‘Evaluable for objective response set’ is added.

A footnote [a] for the definition of measurable disease is added

A footnote [b] with the explanation that DLT analysis set will be derived from SRC meeting minutes is added.

A paragraph explaining how the patients will be selected for each analysis set, prior to data base lock is added.

Within Table 3 Added ‘Evaluable for objective response’ as an analysis set for efficacy endpoints except for progression free survival (PFS) and (OS).

Section 2.3 (previously section 2.2)

Added following sentence
The global pandemic (Covid-19) related important protocol deviations will also be captured and reported as per latest corporate standards

Changed 'with regard' to 'regarding'

Moved the following sentence from second paragraph of this section to the beginning of the third paragraph

The above list of protocol deviations is not exhaustive and additional important deviations will be added prior database lock as required.

Corrected patients ‘skip a dose’ to ‘miss a dose’.

Corrected the second bullet point in such a way that missing a single safety assessment which having a potential implication to patient safety will be classified as important protocol deviation.

Based on section 9.4.3, PDc analysis will be presented in a separate document.

Section 3.1

Revised the data cut off specification as follows:

Data analysis will be performed separately for each module, study part or cohort, and a CSR may be written for each module separately.

Revised the entire section with an explanation to the reference date for safety analysis and efficacy endpoints.

Revised the Time Window table 4
Corrected 'half way' to halfway'
Corrected 'visit based' to 'visit-based'

Visit windowing for radiological tumour evaluations added.
Deleted the medical history, and tumour evaluations from the handling missing data section. The missing date won’t be imputed for both medical history any tumour evaluations.

Section 3.2.1.1

added a ','

Section 3.2.1.3

Revised the title

Section 3.2.1.4

All casually related AEs are replaced with possibly related AEs as per AZ standard.

Section 3.2.15

Revised the to indicate the latest WHO dictionary standard will be used for the study summary reporting.

Section 3.2.1.6

AstraZeneca reference range for vital signs table added to the section.

Section 3.2.1.7

The list of laboratory safety variable table added.

Section 3.2.1.8 Added a new section for

Creatinine clearance formula added

The estimated Creatinine Clearance is will be calculated based on by using Cockcroft-Gault equation as follows.:

CrCl={((140–age) x weight)/(72xSCr)} Multiply by 0.85 (if patient is female)

CrCl (creatinine clearance) = mL/minute

Age = years

Weight = kg (the last weight measured closest to the time when serum creatinine is measured)

SCr (serum creatinine) = mg/dL

Section 3.2.1.9

Updated with the list of variables to be considered for physical examination summary tables.

Section 3.2.1.10

The AZ defined reference range for ECG variables added as Table 7.

Section 3.2.1.11

Revised the sentence as follows:
Change of left ventricular ejection fraction (LVEF) from baseline will be calculated at each scheduled post-baseline assessment time and summarised as follows.

Section 3.2.2.1

Added a new section 3.2.2.1 with tumour response criteria

Added a new paragraph as follows:
The modules require RECIST results, the RECIST tumour response data will be used to determine each patient's visit response according to RECIST version 1.1 as well as the mRECIST criteria. It will also be used to determine when a patient has progressed in accordance with RECIST and also their best objective response to study treatment.

Section 3.2.2.1.1

Expanded step 3 in TL visit responses subsequent to CR section follows:
If not all lesions meet the CR criteria (i.e., a pathological lymph node is selected as TL has short axis ≥ 10 mm or the reappearance of previously disappeared lesion) or a new lesion appears, then response will be set to PD.

Sentence corrected in Irradiated lesions/lesion intervension
If scaling up is not appropriate due to too few non-missing measurements, then the visit response will be set as NE.

Section 3.2.2.1.2

Changed title to Best Objective Response and added sub sections for RECIST and mRECIST Confirmation criteria for mRECIST PD is moved is added

Section 3.2.2.1.3

A separate section for Best Objective response rate criteria for mRECIST is added.

A sentence is added to the section to that mRECIST is applicable only to immune oncology combinations modules.

BoR will be assessed by mRECIST criteria as follows for immune oncology (IO) combination modules which may be added to the study in future.

The criteria for evaluating tumour response by mRECIST is elaborated with all conditions and scenarios.

Section 3.2.2.1.8

The following criteria added to overall survival endpoint.

OS analysis will be performed only for the part B of the study module.

Section 3.2.2.2

Revised the entire section as per AZ PK standards. Added each plasma and urine parameters required for AZD7846. Added the expansion and abbreviation of all parameters listed.

Diagnostic parameters are also included.

Added a section for plasma 4β-hydroxy cholesterol.

Section 3.2.2.3 and 3.2.2.4

Deleted section for 'calculation or derivation of pharmacodynamic variables'

Section 4.2.5

Changed the abbreviation for pharmacodynamics to PDc (previously PD).

Section 4.2.1

Revised the sentence as follows:

> The post-baseline results and it's change from baseline for laboratory, ECG, vital signs data at each timepoint will be summarised and presented using box plots globally for part A and for Part B of study

Section 4.2.2

Revised and added the following sentence:
A reference line at the –30% change in TL tumour size level, which corresponds with the definition of 'partial' response and another reference line at +20%, corresponds with the definition of 'progressive disease' will be added to the plots.

Section 4.2.3

Revised the entire section for Assessment of pharmacokinetic food effect

Changed the abbreviation for standard deviation to StD (previously SD).

Table 11 with list of descriptive statistics for each parameter required for PK part is added. Added a section for Plasma 4β-hydroxy cholesterol summary requirements.

Section 6

Added the details of the new analysis set defined in this SAP as change in the analysis from protocol.

Version 3.0, 21 January 2022

Section 1.1

Updated with latest versions of protocol and electronic case report form.

The PK abbreviations and definitions are updated from those in the CSP in line with current AZ guidance for PK reporting

Table 4: visit windowing (safety analysis)

Updated the windowing for cycles greater than 3. Increased the analysis Day 1 analysis window from ± 1 to ± 2.

Section 3.2.1.8 Creatinine Clearance

Added summaries to provided in addition to listings.

Section 3.2.1.9

This section is moved from 3.2.2.3 to 3.2.1.9

Previous section 3.2.1.9 re-numbered to section 3.2.1.10

Previous section 3.2.1.10 re-numbered to section 3.2.1.11

A correction was made as follows:

'summarised by visit and by actual treatment group' is replaced with 'summarised by module, by part, by cohort and visit'.

Previous section 3.2.1.11 re-numbered to section 3.2.1.12

A correction was made as follows:

Post baseline summaries by actual value, change from baseline and absolute change from baseline by categories as specified are added.

'summarised by visit and by actual treatment group' is replaced with 'summarised by module, by part, by cohort and visit'.

Previous section 3.2.1.12 re-numbered to section 3.2.1.13

Section 3.2.2.2

Plasma parameters, Urine parameters, and plasma diagnostic parameters are added by study module, by part, by cycle and day in a tabular form

Section 4.1

Added the following criteria for planned arm and actual arm:

The planned dose and the actual dose received by each patient will be closely assessed by study medical monitor and provided in a separate MS Excel sheet, which will be used for study summaries.

Section 4.2.3

Revised the entire section for Assessment of pharmacokinetic food effect

Changed the abbreviation for standard deviation to SD (previously StD).

Table 11 deleted

Replaced gStD with geometric standard deviation or gSD.

Replaced gCV with gCV%

The conditions for PK summary presentation for values > LLOQ replaced with language taken from AZ guidance document

Additional condition for one PK observation > LLOQ is added as follows:

One observation > LLOQ is presented as maximum with other summary statistics as NC.

Table 12 renumbered to Table 11.

Section 6

Language pertaining to addition of evaluable for objective response set for analysis was removed as it is specified in CSP version 5.0.

The PK parameter symbols re-defined in SAP to match with AZ Corporate CSRHLD Reporting Standard v 3.4 is added.

Section 7

Added list of references.

Version 4.0, December 2022

Grammatical, typographical, and formatting updates have been applied throughout the Statistical analysis plan.

Following the sponsor decision to halt development of AZ7648, the required number of tables, figures and listings were reduced to focus primarily on safety, with additional limited efficacy and PK outputs for publication purposes.

The following changes are made to the SAP with respect to the final scope the study.

All references to Part B of Core module, Part B expansion to Combination Module 1 and proposed food effect cohort in Core module were removed from analysis plan.

Removed following sections from previous version of the analysis plan.

Best objective response by modified RECIST (mRECIST)

Section 3.2.2.1.7 Overall survival

Assessment of dose proportionality

Assessment of Pharmacokinetic Food effect

Interim analysis for Part B of the Combination module 1.

Section 1 Introduction : Updated the electronic case report form version to 9.1 (04 August 2022)

Section 2.2 Analysis set: Elaborated in detail how baseline and demographics, safety, pharmacokinetics and efficacy summaries been presented.

For consistency, all previous references to PK set/ PK analysis set were replaced with Pharmacokinetics set.

In the pharmacokinetics analysis sections, all references to ‘dose levels’ were replaced with ‘dose regimens’.

Section 4.2.1

Removed inclusion of box plots for ECG parameters.

Removed inclusion of the summary for 4β-hydroxy cholesterol concentration data

Added a sentence to specify that the change from baseline in all haematological and chemistry parameters would be presented using spaghetti plot.

Removed tlag from PK analysis since food effect cohort is not included in the study.

For consistency all ‘subjects/subject’ were replaced with ‘patients/patient’

1 STUDY OBJECTIVES

1.1 Introduction

This is a modular Phase I/IIa, open-label, multi-centre, study of AZD7648 administered orally, either as a monotherapy, or in combination with either cytotoxic chemotherapies or novel anti-cancer agents in patients with advanced malignancies. The modular design allows for an escalation of the dose of AZD7648 alone or in combination with either cytotoxic chemotherapies or novel anti-cancer agents, with intensive safety monitoring to ensure the safety of the patients.

This statistical analysis plan (SAP) provides the technical elaboration of the statistical analysis of safety, efficacy and pharmacokinetic (PK) data.

Following the sponsor decision to halt development of AZ7648, the required number of summary tables, figures and listings were reduced to focus primarily on safety, with additional limited efficacy and PK outputs for publication purposes.

The analyses described in this SAP are based upon the following study documents:

- Study protocol, Version 5.0 (1 October 2021).
- electronic Case Report Form (eCRF), D9170C00001 v 9.1 (04 August 2022).
- LDMS_001_00201968 Pharmacokinetic Evaluations in Clinical Studies.
- AZ Corporate CSRHLD Reporting Standards v3.4 (31 March 2021).

Specifications for tables, figures and listings are contained in a separate document.

1.2 List of modules

The following modules for the study are included within this SAP.

Core Module: AZD7648 Monotherapy. Part A, dose escalation

Combination Module 1: AZD7648 + PLD. Part A, dose escalation.

For the endpoints included in the safety, efficacy and exploratory objectives, see Table 1.

Table 1 : Study objectives and endpoints

Primary objective (Safety):	**Endpoint/Variable:**
To investigate the safety and tolerability of AZD7648 when given orally to patients with advanced malignancies, as monotherapy and in combination with anti-cancer agents, and define	• Adverse events (AEs)/serious adverse events (SAEs) • Dose limiting toxicities (DLTs) • Physical examination

the doses and schedules for further clinical evaluation.	• Eastern Cooperative Oncology Group performance status (ECOG PS) • Vital signs • Electrocardiogram (ECG) and Echocardiogram (ECHO; applicable for Combination Module 1 only) • Laboratory data
Secondary objectives:	**Endpoint/Variable:**
To characterise the PK of AZD7648, following a single dose and at steady state after multiple dosing, when given orally as monotherapy and in combination with anti-cancer agents.	• Area under the curve to infinity (AUCinf) and/or AUClast after a single dose and AUC□ after multiple doses. • Maximum plasma concentration (Cmax) after single and multiple doses. • Time to reach maximum plasma concentration (tmax) • Minimum plasma concentration at steady state (Cmin) • Half-life (t½λz) • Accumulation ratio (Rac) • Dose proportionality (TCP) • AUClast and Cmax ratio for food effect (applicable for food effect cohort only in the Core module expansion phase) • Other PK parameters may also be estimated
[a]To understand the cytochrome P450 3A4 (CYP3A4) induction potential of AZD7648	Post-dose to pre-dose 4β-hydroxy cholesterol ratio (only for AZD7648 Core Module)
To obtain a preliminary assessment of anti-tumour activity of AZD7648 as monotherapy and in combination with anti-cancer agents	Radiological response evaluated using response evaluation criteria in solid tumours (RECIST 1.1) • Percentage best change in target lesion (TL)

	• Duration of response (DoR) • Objective response rate (ORR) • Progression-free survival (PFS) • Overall Survival (OS) (Part B only)
[b]Tertiary/Exploratory objectives:	**Endpoint/Variable:**
CCI	• CCI • CCI
CCI	• CCI • CCI
CCI	• CCI • CCI CCI

[a] Blood samples will be collected from all patients in AZD7648 monotherapy.

[b] Tertiary/Exploratory objectives are not part of the CSR, thus not explained further in this document.

2 DEFINITION OF ANALYSIS SETS

2.1 Analysis plan

Data analysis will be performed separately for each module or study part and an abbreviated CSR will be written.

2.2 Analysis sets

All patients who receive any amount of study treatment will be included in the safety analysis. For the safety summaries, patients who received study treatment will be presented by module, by part, by cohort and planned starting dose level and dose frequency. Actual dose level and frequency received by patients within each planned cohort will be summarised separately.

For all efficacy analyses, and for baseline and demography summaries, patients are classified according to the module, part, cohorts and the dose they were randomised/assigned to (i.e. the planned treatment/dose level/dose schedule)

The plasma concentrations of AZD7648 and PLD for each scheduled time point will be summarised by module, cohort (dose regimen) and Cycle/PK day (single dose or multiple dose) based on the pharmacokinetics set. The dosing regimen used throughout the PK outputs includes both the dose level and dose frequency of the analyte and should be the planned (protocol scheduled) dosing regimen, although ad hoc summary tables and figures may be requested to include data from patients from a different cohort who were either mis-dosed or where the dose level was the same but the frequency was different (would apply to single dose PK data only).

Details of the analysis sets are presented in Table 2.

Table 2: Analysis sets

Analysis Set	Definition
Enrolled	All patients who signed the informed consent.
Safety set	All patients who received at least 1 dose of any study treatment
Pharmacokinetics (PK) set	All patients who received at least 1 dose of any study treatment with at least one reportable post first dose

	concentration without any protocol deviations that might affect PK.
Evaluable for objective response set	All patients who had a measurable baseline disease[a] by RECIST 1.1 assessment and received at least one dose of any study treatment.
Evaluable for efficacy set	All patients who received at least 1 dose of any study treatment and have a baseline tumour assessment according to RECIST 1.1.
DLT evaluable set[b]	All patients who received at least 1 dose of any study treatment and either experienced DLT during the cycle 0 or 1, or who completed minimum safety evaluation requirements and has received at least 75% of the total amount of planned dose of AZD 7648 (and PLD for combination Module 1). In the event of an intra-patient dose escalation, such patients will not be evaluable for DLT at the escalated dose.
Pharmacodynamics set	All patients who received at least 1 dose of of any study treatment with at least one reportable pharmacodynamic measurement

[a] Measurable disease is defined as having at least one measurable target lesion, not previously irradiated, which is ≥ 10 mm in the longest diameter (LD) (except lymph nodes which must have short axis ≥ 15 mm).

[b] This will be derived directly from the most recent safety review committee meeting minutes prior to data cut off.

Upon database release for each module, protocol deviations and analysis set outputs will be produced and will be sent to AZ for review. Prior to database lock, an analysis set classification meeting will be arranged to discuss the outputs and decide which patients and/or patient data will be excluded from certain analyses. Decisions made regarding the exclusion of patients and/or patient data from analyses will be made prior to database hard lock and will be documented and approved by AZ.

A summary on which analysis set will be used for each outcome variable is provided in Table 3.

Table 3: Summary of outcome variables and analysis sets

Outcome variable	Analysis Sets
Disposition	Enrolled
Demography and baseline characteristics	Safety
Safety data	
Exposure	Safety
Adverse Events	Safety
Prior/Concomitant Medication	Safety
Laboratory measurements	Safety
Vital Signs/ECG/Physical examination	Safety
Echocardiogram	Safety
ECOG PS	Safety
DLTs	DLT evaluable set
4β-hydroxy cholesterol ratio in plasma	Pharmacokinetics set
Efficacy Data	
Best Objective Response	Evaluable for objective response set Evaluable for efficacy set
Objective Response Rate	Evaluable for objective response Evaluable for efficacy set
Change in tumour size	Evaluable for objective response
Duration of Response	Evaluable for objective response Evaluable for efficacy
PFS	Safety /Evaluable for efficacy
Overall survival	Safety
Pharmacokinetics	
Pharmacokinetic concentrations and parameters	Pharmacokinetics set
Pharmacodynamics	
PDc analysis will be presented in a separate document.	PDc related population will be defined in a separate document dedicated to PDc.
Exploratory biomarkers	

Outcome variable	Analysis Sets
CCI [redacted] CCI [redacted]	CCI [redacted]

2.3 Protocol deviations

A list of all protocol deviations 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 following general categories (not an exhaustive list) may be considered as important protocol deviations (IPDs) and will be programmatically derived by data management from the electronic case report form (eCRF) and impact harmony data, unless otherwise stated. These will be summarised and listed in the CSR as appropriate. All study specific IPDs will be summarised and listed as per latest corporate reporting standards. Global pandemic (Covid-19) related IPDs will be listed only.

- Patients who deviate from key entry criteria per the CSP.
- Patients who received a different dose than their assigned one or miss a dose.
- Patients missing important protocol required safety assessments (vital signs, clinical chemistry / haematology parameters, urinalysis, ECGs, sample collection for PK etc.) and having potential important impact on patient safety. Baseline RECIST scan missing or > 28+ days before treatment assignment.
- Baseline RECIST scan missing for > 28 + days before treatment assignment.
- No baseline RECIST 1.1 assessment on or before the date of treatment assignment or no baseline bone scan assessment on or before date of treatment assignment.
- Received prohibited anti-cancer therapy during study treatment period.
- Changes to the procedures that impact the quality of the data or any circumstances that can alter the evaluation of the PK (e.g., sampling processing errors that lead to inaccurate bioanalytical results and incomplete PK profile collects).
- Met study treatment discontinuation criteria but continued study treatment and potentially had major impact to patients' safety according to clinical judgement.

The above list of protocol deviations is not exhaustive and additional important deviations may be added prior to database lock as required. A complete list of important protocol deviations can be seen in PD specification document. The categorisation of the above as important deviations is not automatic and will depend on duration and the perceived effect on safety, efficacy, or evaluability of PK profile. If a patient has a deviation that is considered to critically impact upon PK, affected PK data of that patient will be excluded from summaries and statistical analysis (unless otherwise specified), but will still be reported in the listings. Except for certain deviations affecting PK, deviations will not generally lead to exclusion from the analysis sets. However, the impact on the primary endpoint will be assessed, and if considered necessary sensitivity analysis may be considered. All the important protocol deviations will be summarised for the safety analysis set. During the study, decisions on how to handle errors in treatment dispensing (regarding continuation/discontinuation of study treatment or, if applicable, analytically) will be made on an individual basis with written instruction from the study team leader and/or statistician.

In addition to the programmatic determination of the deviations above, other study deviations captured from the CRF module for inclusion/exclusion criteria will also be summarised and listed for protocol deviation reviews. All other deviations that are not important protocol deviations will be termed 'Other Study Deviations'. Any other deviations from monitoring notes or reports will be reported in an appendix to the CSR.

3 DESCRIPTION OF VARIABLES

3.1 General principles

Data cut off

Data analysis will be performed separately for each module, study part or cohort, and a CSR may be written for each module separately. One administrative analysis is planned see Section 5.

Baseline measurements and change from baseline variables

Baseline (for both safety and efficacy assessments) will be the last non missing value obtained prior to the first dose administration of study medication on cycle 0 day 1. Any information taken after first dose of study medication on cycle 0 day 1 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 best value would be taken

as baseline as this is the most conservative. In the scenario where there are two assessments on cycle 0 day 1, one with time recorded and the other without time recorded, the one with time recorded would be selected as baseline. If no value exists before the first dose/administration, then the baseline value will be treated as missing.

In all summaries change from baseline variables will be calculated as the post baseline value minus the value at baseline.

Percentage (%) change from baseline= [(post baseline value – baseline value) / baseline value] × 100.

Study day

The study day describes the day of the event or assessment date, relative to the reference start date. The study day is calculated as:

- The date of the event (i.e. visit date, onset date of an event, assessment date etc.) – reference start date+1 if the event is on or after the reference start date;
- The date of the event (i.e. visit date, onset date of an event, assessment date etc.) – reference start date if event precedes the reference start date.

The reference date for all assessments except for tumour assessments, will be the start of the study treatment in cycle 0 (i.e., cycle 0, day 1). There is no study day 0 for this study. Date of cycle 1, day 1 dosing will be considered as the start date for the calculation of efficacy endpoints (tumour response, PFS), which follows CSP visit window starting from cycle 1, day 1. The study day will be displayed in the data listings. If an event starts before the reference start date, the study day displayed on the listing will be negative.

Time Windows

Time windows will need defining for any presentations that summarise values by visit.

Given the washout period between Cycle 0 and Cycle 1 can vary between patients (3-7 days per CSP) and therefore study day of Cycle 1 Day 1 onwards will vary, for the purposes of windowing assessments the study day of visits from Cycle 1 Day 1 onwards will be adjusted in order to allow the same window to be applied across patients. This will not impact on study day displayed in listings and will be used only by programming as an intermediate step to assign analysis visits. The amount to adjust the study day by will be derived assuming the planned day for Cycle 1 Day 1 is day 8 for all patients:

Adjustment (days) = 8 – actual Cycle 1 Day 1 study day

Study day for all safety assessments from Cycle 1 Day 1 onwards will be adjusted by this amount when assigning assessments to analysis visits. Actual, unadjusted study day will be presented in listings.

The following conventions should apply:

- Inclusion within the time window should be based on the actual date and not the intended date of the visit.
- The visit window following baseline will be constructed as per Table 4 for the safety assessments
- For summaries showing the maximum or minimum values, the maximum/minimum value recorded on treatment will be used (regardless of where it falls in an interval).
- Listings should display all values contributing to a time point for a patient.
- Often the most meaningful summaries focus on extreme values rather than summaries at each visit but if summaries over time are felt to be required:
- 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 summarised, 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.

Table 4: Visit windowing (safety analysis)

Cycle	Target Day	Analysis visit	Analysis Visit Window
	screening	Baseline	Day -28 to Cycle 0 Day 1 (pre-dose)
C0	Day 1 (pre-dose)		No analysis visit window: First day of intake of AZD7648

C0	Day 2	Cycle 0 Day 2	C0D1 + 1 day
C0	Day 3	Cycle 0 Day 3	C0D1 + 2 days
C0	Day 4	Cycle 0 Day 4	C0D1 + 3 days
C1	Day 1	Cycle 1 Day 1	No analysis visit window: Monotherapy: First day of restart of AZD7648 after C0 Combinations: Day 1 of associated anticancer agent or first day of restart of AZD7648 after C0 whichever comes first
C1	Day Y	Cycle 1 Day Y	If Y=3 then Day 2 to Day 4 If Y=7 then Day 2 to Day 7
C1	Day 8	Cycle 1 Day 8	[a]Last day of previous interval + 1 day to Day 11
C1	Day 15	Cycle 1 Day 15	Day 12 to Day 18
C1	Day 22	Cycle 1 Day 22	Day 19 to C2D1 – 2 days if following cycle Otherwise Day 19 to C1D1+26 days (last cycle)
C2	Day 1	Cycle 2 Day 1	From: Monotherapy: C1D1 + 28 – 1 day or (first day of intake of AZD7648 after C1D1+28) - 1 day; if AZD7648 is off on C1D1+28-1 day. Combinations: (Day 1 of associated anticancer agent for C2 or C1D1 + 28) – 1 day; if associated anticancer agent stopped;

			or (first day of intake of associated anticancer agent after C1D1+28) – 1 day; if associated anticancer agent is off since C1D1+28-1 day To: Monotherapy: C1D1 + 28 + 1 day or (first day of intake of AZD7648 after C1D1+28) +1 day if AZD7648 is off on C1D1+28-1 day Combinations: (Day 1 of associated anticancer agent for C2 or C1D1 + 28) +1 day; if associated anticancer agent stopped. or (first day of intake of associated anticancer agent C1D1+28) +1 day; if associated anticancer agent and off on C1D1+28-1 day.
C2	Day 15	Cycle 1 Day 15	C2D1 + 11 day to C2D1 + 17 days
Cx (≥3)	Day 1	Day1 of any cycle ≥ 3	From: Monotherapy: Cx-1D1 + 28 – 2 days or first day of intake of AZD7648 after Cx-1D1+28) – 2 days; if AZD7648 is off on Cx-1D1+28-1 day. Combinations: (Day 1 of associated anticancer agent for Cx or Cx-1D1 + 28) -2 days; if associated anticancer agent stopped or

			(first day of intake of associated anticancer agent after Cx-1D1+28) – 2 days; if associated anticancer agent is off on Cx-1D1+28-1. To: Monotherapy: Cx-1D1 + 28 + 2 days or first day of intake of AZD7648 +1 day after C1D1+28; if AZD7648 is off on C1D1+28-1 day. Combinations: (Day 1 of associated anticancer agent for Cx or Cx-1D1 + 28) +2 days; if associated anticancer agent stopped. or (first day of intake of associated anticancer agent after Cx-1D1+28) +2 days; associated anticancer agent is off on Cx-1D1+28-1 day.
-	-	IP Disc[b]	IP Disc + 1 day
		28 day safety follow-up after IP Disc	IP Disc +28 -7 days To ID Disc + 28 +7 days

[a] Previous interval is C1D1.

[b] Investigational product discontinuation.

Visit windowing for radiological tumour evaluations

The radiological tumour assessments done within 28 days prior and up to pre-dose on cycle 0 day 1 will be considered as baseline. In case of multiple evaluations in the above time period, the value closest to cycle 0, day 1 will be taken as baseline.

A windowing rule will be applied and will follow the protocol allowed visit window; therefore, any RECIST scan performed within ± 1 week of the protocol scheduled visit will be used for that visit. Given

scans will be done relative to Cycle 1 Day 1, the adjustments described for safety assessments will be done when windowing target lesion data.

Handling Missing data

No missing data will be imputed with the exception of the imputation rules described below.

Imputation for partial dates of adverse events, concomitant medication and death

Start and stop dates are collected on the CRF and measures will be taken to minimize missing in data collection. In case of partial information in these dates, the following rules will be used to impute the dates.

If start date is partial:

- Missing day - impute the 1st of the month unless month is same as month of first dose of study drug then impute first dose date.
- Missing day and month – impute 1st January unless year is the same as first dose date then impute first dose date.
- Completely missing – impute with date of first dose of the study treatment, unless the end date suggests it could have started prior to this in which case impute with 1st January of the same year as the end date.
- Imputed start date should be no later than the end date.

For 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. Imputed dates will be used in the calculation of time since diagnosis.

If stop date is partial:

- Missing day - Impute the last day of the month unless both the month and the year are the same as the last dose date or the planned analyses data cut-off date, then impute the last dose date or the planned analyses data cut-off date.
- Missing day and month – impute 31st December unless the year is the same as the last dose date or the primary analysis data cut-off date then impute the last dose date or the primary analysis data cut-off date.
- 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).

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 unless otherwise specified.

- If a patient 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 when the date is completely missing. Otherwise, the death date using the available information provided:
    a. For Missing day only – using the 1st of the month
    b. For Missing day and Month – using the 1st of January

Imputation for Laboratory Values Outside of Quantification Range

Missing safety data will generally not be imputed. However, safety assessment values of the form of "< x" (i.e., below the lower limit of quantification) or > x (i.e. above the upper limit of quantification) will be imputed as "x" in the calculation of summary statistics but displayed as "< x" or "> x" in the listings. Values of "<=x" or ">=x" will be imputed as well. Note that 0 should not be used as an imputed value in case the endpoint requires a log transformation.

Time unit

A year length is defined as 365.25 days. A month length is 30.4375 days (365.25/12). If duration is reported in months, duration in days will be divided by 30.4375. If duration is reported in years, duration in days will be divided by 365.25.

3.2 Outcome variables

3.2.1 Primary Outcome Variables

The primary outcome variables which address the safety and tolerability of AZD7648 monotherapy or with a specific combination partner are described in Section 3 of the Clinical Study Protocol.

3.2.1.1 Duration of Exposure

Extent of exposure for AZD7648 and PLD will be defined in terms of the number of days the treatment is received.

Exposure (i.e., duration of treatment) will be defined as follows:

1. Total treatment duration (if IP not discontinued after the last dose > 0 mg) = (min (last dose date where dose > 0 mg + **Z**, date of death, date of DCO) − date of first dose +1).

2. Total treatment duration (if IP discontinued after the last dose > 0 mg) = (min (last dose date where dose > 0 mg, date of death, date of DCO) − date of first dose +1).

    - If the planned schedule is continuous (28 days) intake (core module), Z=0
    - If the planned schedule is to take continuously for the first 7 days in the cycle, Z=21

    The planned schedule of PLD dosing is once at the start of each cycle, Z=27

    Similar imputation rule will be used for counting the duration of dose interruption.

3. Actual treatment duration = total treatment duration, excluding dose interruptions not in accordance with the protocol, and any planned no dose periods.

Exposure will also be measured by the number of cycles received. A cycle corresponds to a period of 28 days. 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.

Where total exposure will be calculated as above, and a dose interruption is defined as any length of time (number of days) where the patient has not taken any of the planned daily dose.

Missed or forgotten doses

Missed and forgotten doses should be recorded on the dosing page as a dose interruption with the reason recorded as "Patient forgot to take dose". 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 recorded administration of study medication will be used in the programming.

3.2.1.2 Relative dose intensity

Dose intensity of AZD7648 and PLD will be addressed by considering relative dose intensity (RDI). Relative dose intensity (RDI) is the percentage of the actual dose delivered relative to the intended dose through to treatment discontinuation. Relative dose intensity (RDI) will be defined as follows:

RDI (%) =100* d/D,

where

d the actual cumulative dose delivered up to the actual last day of dosing based on the study treatment schedule and

D is the intended cumulative dose up to the actual last day of dosing based on the study treatment schedule. D is the total dose that would be delivered, if there were no modification to dose or schedule.

If a participant permanently discontinues study treatment, then the date of last administration of study medication recorded on eCRF will be used to program the RDI. If a participant permanently discontinues study treatment during a treatment interruption, then the date of last administration of study medication recorded on DOSEDISC of the eCRF will be used to program the RDI.

The actual treatment duration, total treatment duration and RDI will be summarised. Exposure swimmer plot will be produced, with a line presented for each participant to display relevant exposure and disposition details.

3.2.1.3 Dose limiting toxicities (DLTs) and patients evaluable for DLTs

A patient will be defined as evaluable if they have completed the DLT evaluation period with sufficient dosing, at least 75% of the total amount of planned dose of AZD7648 (and PLD for combination module 1). Additionally, patients who have a DLT are considered evaluable. Patients who withdraw from the study prior to completion of the first 28 day safety observation period for reasons other than a DLT will not be considered evaluable.

At each SRC meeting, the patients in the current dose escalation cohort are reviewed by the SRC, the SRC will agree on the patients who are evaluable or have a DLT following Section 6.1.3 of the CSP. The evaluable patients will be used by the SRC to inform the next dose decision.

See Section 6.1.3 of the Clinical Study Protocol for the definition of a DLT. For reporting purposes, the DLTs and the list of DLT evaluable patients are as approved and documented at the Safety Review Committee meetings.

3.2.1.4 Adverse Events

Adverse events (AEs) and serious adverse events (SAEs) will be collected throughout the study, from date of informed consent until 28 days after the last dose of study treatment. Events will be defined as treatment emergent if they onset, or worsen (by investigator report of a change in intensity), during the

treatment period starting from the first dose on cycle 0, day 1 or during the 28-day safety follow-up period. Any events in this period that occur after a patient has received further therapy for cancer (following discontinuation of study treatment) will be flagged in the data listings. The latest version of MedDRA will be used to code the AEs. AEs will be graded according to the National Cancer Institute of Common Terminology Criteria for AEs (CTCAE version 5.0 or higher).

In general, all AE summary tables include only treatment emergent AEs. AEs occurring prior to dosing or starting more than 28 days after discontinuation of study drug will be flagged in listings and will not be included in any summaries.

All reported AEs will be listed along with the actual treatment received at the time of onset, date of onset, date of resolution (if AE is resolved), investigator's assessment of CTCAE grade, relationship to study treatment, action taken and outcome. Frequencies and percentages of patients reporting each preferred term will be presented (i.e., multiple events per patient will not be accounted for, except for event level summaries).

Summaries of adverse events (the number and percentage of patients by treatment) by MedDRA System Organ Class (SOC) and Preferred Term (PT) will include but are not limited to:

- All AEs.
- All AEs possibly related to study treatment.
- AEs of CTCAE grade 3 or higher.
- AEs of CTCAE grade 3 or higher, possibly related to treatment.
- AEs with outcome of death.
- All SAEs.
- All SAEs possibly related to study treatment.
- AEs leading to discontinuation of treatment.
- AEs leading to discontinuation of treatment, possibly related to treatment.
- SAEs leading to discontinuation of treatment.
- SAEs leading to discontinuation of treatment, possibly related to treatment.

Other significant adverse events (OAE)

No OAEs are planned to be defined for this study.

3.2.1.5 Prior/Concomitant Medications and procedures

The latest version of World Health Organization Drug Dictionary (WHODD) will be used to code any medications and the version used will be clearly stated as footnote in the summary tables. Allowed concomitant medication will be summarised by anatomical therapeutic chemical (ATC) level classification, by generic term. Concomitant procedures will be summarised by system organ class, by MedRA preferred term.

3.2.1.6 Vital Signs Changes

Changes from baseline in vital signs to each post-baseline assessment will be calculated. Absolute values, changes from baseline and percentage change from baseline will be summarised by module, by part, by cohort and visit.

There will be no imputation for missing values. Observed values and changes from baseline will be compared to the relevant AstraZeneca defined reference ranges for vital signs (see Table 5: AstraZeneca defined reference ranges for vital signs variables and clinically important change criteria and all values (observed and change) falling outside the reference ranges will be flagged in the listings.

Table 5: AstraZeneca defined reference ranges for vital signs variables

Vital sign (unit)	Outside AZ defined reference range lower limit if	Outside AZ defined reference range upper limit if	Treatment emergent decrease if	Treatment emergent increase if
SBP (mmHg)	<100	>160	<-30	>30
DBP (mmHg)	<60	>100	<-15	>15
Pulse	<40	>100	<-20	>20
Height (cm)	<140	>220		
Weight (kg)	<40	>200		

SBP- systolic blood pressure; DBP-diastolic blood pressure.
mmHg-millimeter of mercury; cm-centimeter; kg-kilogram.

3.2.1.7 Laboratory Data

All laboratory results collected will be listed.

Summaries for safety laboratory will only include the parameters specified in Table 6.

All values will be classified as low (below range), normal (within range), or high (above range) based on local laboratory reference ranges. Results will be converted to standard units and graded with CTCAE version 5.0. A shift table from baseline to maximum value will be summarised for urinalysis variables. Maximum post-baseline CTC grade will also be calculated.

If the same parameter is found as measured in serum and in plasma, then the summaries will not distinguish between them (e.g. values from plasma albumin and serum albumin will be summarised under albumin). If the same parameter is found as measured in serum and in plasma within the same patient, which would be a rare case, then the change from baseline will only be calculated for those post-baseline values using the same source, i.e., only within plasma or serum. If one patient has multiple toxicity grades, because they are derived separately from serum and plasma then the maximum value of the two will be considered.

For all continuous laboratory assessments, absolute value, change from baseline and percentage change from baseline will be summarised using descriptive statistics at each scheduled assessment time by actual treatment group.

For clinical chemistry and haematology, shift tables will present movements from baseline to worst value on-treatment (defined from start of treatment to biopsy day) according to reference range classification. CTCAE grade changes from baseline to on-treatment will also be provided. Corresponding shift tables ("Negative", "Trace", "Positive", "0", "+", "++", "+++") will be produced for urinalysis. In addition, the number of patients with ≥ 2 CTCAE grade changes and CTCAE grade changes to 3 or 4 will be summarised by actual treatment group for clinical chemistry and haematology parameters.

Plots for both maximum post-baseline alanine transaminase (ALT) and aspartate transaminase (AST) versus the maximum post-baseline total bilirubin (expressed as multiples of their upper limit of normal [ULN] reference range) will be produced with reference lines at 3 x ULN for ALT and AST and 2 x ULN for total bilirubin. Spaghetti plots of absolute values and change from baseline values for all haematology and clinical chemistry parameters will also be presented.

Liver biochemistry test results over time for patients who show elevated ALT or AST (≥ 3 x ULN) and elevated bilirubin (≥ 2 x ULN) (elevated results do not need to be present at the same visit) or ALT or AST of ≥ 5 x ULN, will be tabulated and plotted.

Table 6: Laboratory safety variables

Haematology/Haemostasis (whole blood)	Clinical Chemistry (serum or plasma)
B-Haemoglobin (Hb)	S/P-Creatinine

B-Leukocyte count	S/P-Bilirubin, total
B-Leukocyte differential count (absolute count) [a]	S/P-Alkaline phosphatase
B-Platelet count	S/P-Aspartate transaminase
B-Reticulocyte count	S/P-Alanine transaminase
Coagulation	S/P-Albumin
INR	S/P-Potassium
Activated Partial Thromboplastin Time (APTT)	S/P-Calcium, total
Urinalysis (dipstick)	S/P-Sodium
U-Hb/Erythrocytes/Blood	S/P-Urea nitrogen
U-Protein/Albumin	S/P-Phosphate
U-Glucose	S/P-Magnesium
	S/P-Gamma-glutamyl transferase
	S/P-Total protein
	Thyroid stimulating hormone (TSH) [b]
	C-reactive protein (CRP) [b]
	Tumour markers

[a] If absolute differentials are not available, % differentials (differential includes neutrophils, lymphocytes, monocytes, basophils, eosinophils) will be provided.

[b] TSH to be measured at baseline and every 3 cycles. CRP to be collected at baseline, then on Day 1 from Cycle 1. Urinalysis at Cycle 0, Cycle 0+1 and Day 1 of each cycle. Tumour markers (if relevant) to be measured at baseline and on Day 1 of every cycle from Cycle 1 (only if elevated at baseline).

3.2.1.8 Creatinine Clearance

The estimated Creatinine Clearance will be calculated using Cockcroft-Gault equation as follows:

C_{Cr}={((140–age) x weight)/(72xS_{Cr})} Multiply by 0.85 (if patient is female)

C_{Cr} (creatinine clearance) = mL/minute

Age = years

Weight = kg (the last weight measured closest to the time when serum creatinine is measured)

SCr (serum creatinine) = mg/dL.

Creatinine clearance will be summarised and listed by cohort, by visit.

3.2.1.9 Plasma 4β-hydroxy cholesterol

For the core module only, individual 4β-hydroxy cholesterol concentration data by cohort, by visit will be listed.

3.2.1.10 Physical Examination

A complete physical examination will be performed at visits specified in schedule of assessments for each module; baseline height, weight, body mass index (BMI) and BMI category (< 18.5, 18.5 - < 25, 25 - < 30, ≥ 30) will be summarised. All physical examination findings will be listed as well.

All abnormal findings from the physical exam will be summarised and reported under AEs.

3.2.1.11 ECG

All ECG data received will be presented in data listings.

Absolute values, changes from baseline and percentage change from baseline to each scheduled visit will be summarised by module, by part, by cohort and visit for the following ECG variables: heart rate, QT interval corrected for heart rate using Fridericia's formula (QTcF), RR, PR, QRS, and QT. The average of the three individual tracings will be used in summaries. However, the individual tracings will be displayed in the data listings.

Number and percentage of patients with QTcF results in each of the following categories will be summarised:

- greater than AstraZeneca Cardiac SKG upper reference range at any time on treatment.
- absolute value> 450 msec.
- absolute value> 480 msec.
- absolute value> 500 msec.
- change from baseline > 30 msec.
- change from baseline > 60 msec.
- absolute value > 450 msec and change from baseline > 30 msec.
- absolute value > 500 msec and change from baseline > 60 msec.

3.2.1.12 Echocardiogram

left ventricular ejection fraction (LVEF) is collected for all patients in combination module 1. Change of LVEF from baseline will be calculated at each scheduled post-baseline assessment time and summarised by part, by cohort and visit..

The absolute change from baseline will also be summarised by following categories:

- Any increase
- No change
- Any decrease
- 0 to <10% decrease
- 10 to <20% decrease
- ≥20% decrease
- ≥10% decrease and ≥ Lower Limit Normal (LLN)

- ≥10% decrease and < LLN
- ≥20% decrease and ≥ LLN
- ≥20% decrease and < LLN

3.2.1.13 Eastern Cooperative Oncology Group performance status (ECOG PS)

ECOG PS status will be summarised and listed by grade (0-4) for each visit.

3.2.2 Secondary Outcome Variables

3.2.2.1 Calculation or derivation of tumour response variables

3.2.2.1.1 RECIST visit responses

For all patients, the RECIST tumour 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 tumour assessments are to be performed no more than 28 days before the first dose/administration of study medication on cycle 1, day 1 and ideally as close as possible to the start of study treatment. Tumour assessments are then performed every 8 weeks (± 1 week) following start of study treatment on cycle 1, day 1 until confirmed 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 tumour response data will be used to determine each patient's visit response according to RECIST version 1.1. At each visit, patients will be programmatically assigned a RECIST 1.1 visit response of complete response (CR), partial response (PR), stable disease (SD) or partial disease (PD) (see Table), using the information from target lesions (TLs), non-target lesions (NTLs) and new lesions and depending on the status of their disease compared with baseline and previous assessments. If a patient has had a tumour assessment which cannot be evaluated, then the patient will be assigned a visit response of not evaluable (NE) (unless there is evidence of progression in which case the response will be assigned as PD).

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

In addition, the objective tumour response assessment will also be assessed for exploratory analysis on a modified RECIST 1.1 criteria considering progression only when confirmed. If progression is not confirmed, then the overall visit response as per modified RECIST should be assessed as SD/ PR or CR and the patient should continue scheduled RECIST 1.1. CT/MRI scans. If progression is confirmed the overall visit response should be assessed as progressive disease as per modified RECIST.

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, 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 the absence/presence of new lesions. If a patient does not have measurable disease at baseline, then the TL visit response will be not applicable (NA).

Table 7: 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.

Visit Reponses	Description
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.

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; it had a BL measure of 29.3cm. The sum of lesions 1-4 at the follow-up is 26 cm. The sum of the corresponding lesions at nadir visit is 26.8 cm.

Scale up as follows to give an estimated TL sum of 28.4cm:

$$\frac{26}{26.8} \times 29.3 = 28.4 \text{ cm}$$

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.

Lymph nodes

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

TL visit responses subsequent to CR

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

- Step 1: If all 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 the sum of diameters for lymph node short axis increases by 20% but all lymph node TL remain < 10mm.
- 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, when referencing the sum of TL diameters, the criteria for PD are also met.
- Step 3: If not all lesions meet the CR criteria (i.e., a pathological lymph node is selected as TL has short axis ≥ 10 mm or the reappearance of previously disappeared lesion) or a new lesion appears, then response will be set to PD.
- Step 4: If after steps 1 – 3 a response can still not be determined the response will be set to remain as CR

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, if appropriate 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 / embolisation), should be handled in the following way and once a lesion has had

intervention then it should be treated as having intervention for the remainder of the study noting that an intervention will most likely shrink the size of tumours:

- Step 1: the diameters of the TLs (including the lesions that have had intervention) will be summed and the calculation will be performed in the usual manner. If the visit response is PD this will remain as a valid response category.
- Step 2: If there was no evidence of progression after step 1, treat the lesion diameter (for those lesions with intervention) as missing and if ≤ 1/3 of the TLs have missing measurements then scale up as described in the 'Scaling' section below. If the scaling results in a visit response of PD then the patient would be assigned a TL response of PD.
- Step 3: 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 have a value of 0 (or < 10mm for lymph nodes) recorded. If scaling up is not appropriate due to too few non-missing measurements, 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).

Lesions that split in two

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

Lesions that merge

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

Change in method of assessment of TLs

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 – site investigator data

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

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

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

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 tumour.

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.

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 overly affect the derivation. This scenario (i.e. whereby new lesion response is NE), should only occur in exceptional cases, as missing data for the new lesion field should always be queried.

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 tumour assessments where possible until objective disease progression is observed.

Table 8: 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.

Visit Responses	Description
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

Overall visit response

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

Table 7: 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

3.2.2.1.2 Best objective response

Best objective response (BoR) is calculated based on the overall visit responses from each RECIST 1.1 assessment. (see Section 3.2.2.1.1). It is the best response a patient has had following first dose of study treatment on cycle 1, day 1; but prior to starting any subsequent cancer therapy or 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 1.1 using the following response categories: CR, PR, SD, PD and NE.

The confirmation of CR or PR should be performed at the next RECIST assessment and must not be less than 4 weeks later. For determination of a best response of SD, the earliest of the dates contributing towards an overall visit assessment will be used. SD should be recorded at least 8 weeks minus 1 week (to allow for an early assessment within the assessment window), after first dose/administration of study medication at cycle 1. For CR/PR, the initial overall visit assessment which showed a response will use the latest of the dates contributing towards an 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 the respective analysis set.

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 post-baseline, if the death occurs ≤17 weeks (i.e., 16 weeks + 1 week to allow for a late assessment within the assessment window) after first dose/administration of study medication at cycle 1, day 1, then BoR will be assigned to the progression (PD) category. For patients who die with no evaluable RECIST assessments, if the death occurs >17 weeks after start of treatment at cycle 1 then BoR will be assigned to the NE category.

3.2.2.1.3 Objective response rate

ORR is defined as the percentage of patients who have a confirmed visit response of CR or PR prior to any evidence of progression (as defined by RECIST 1.1 or confirmed progression by modified RECIST) and will be based on all treated patients with a baseline disease assessment and a subset of all treated patients with measurable disease at baseline separately.

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 a RECIST progression; and receive a subsequent anti-cancer therapy (note that for this study radiotherapy is not considered a subsequent anti-cancer therapy) and then respond will not be included as responders in the ORR (i.e., both visits contributing to a response must be prior to subsequent therapy for the patient to be considered as a responder).

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

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

Similarly, if a patient has three consecutive visit responses of CR, NE, CR, if the time between the 2 visits of CR is greater than 4 weeks, a best response of CR will be assigned.

3.2.2.1.4 Duration of response

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

3.2.2.1.5 Change in target lesion tumour size

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

Tumour size is the sum of the longest diameters (or short axis measurements for lymph nodes) of the target lesions. Target lesions are measurable tumour lesions. Baseline for RECIST is defined to be the

last evaluable assessment prior to starting treatment. The percentage change in target lesion tumour size at each week x for which data are available will be obtained for each patient taking the difference between the sum of the target lesions at each week x and the sum of the target lesions at baseline divided by the sum of the target lesions at baseline multiplied by 100 (i.e. (week x - baseline)/baseline * 100).

Only patients with measurable disease at baseline will be included in summaries of best percentage change in tumour size.

3.2.2.1.6 Progression Free Survival

PFS is defined as the time from first dose of Cycle 1 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 PFS event or censoring – date of first dose + 1). Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST assessment. However, if the patient progresses or dies after two or more missed visits, the patient will be censored at the time of the latest evaluable RECIST 1.1 assessment prior to the two missed visits.

If the patient has no evaluable post-baseline visits or does not have baseline data they will be censored at Day 1 unless they die within 2 visits of baseline (16 weeks plus 1 week allowing for a late assessment within the visit window).

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

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

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

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

3.2.2.2 Calculation or derivation of pharmacokinetic variables

The PK analyses of the plasma and urine concentration versus time data for AZD7648 will be performed by Covance (now Labcorp) Clinical Pharmacology Alliance, on behalf of the Sponsor and will be calculated in accordance with AstraZeneca Guidelines for PK Evaluations in Clinical Studies.

The PK parameters will be derived using non compartmental methods in Phoenix® WinNonlin® Version 8.1 or higher (Certara).

PK analysis will, where data allow, be carried out using actual elapsed times determined from the plasma PK sampling and dosing times recorded in the database. If actual elapsed times are missing, nominal times may be used. Nominal sampling times may be used for any agreed interim PK parameter calculations or graphical visualization of PK data.

The Ae will be calculated using a urine density of 1.0 g/mL. Urine concentrations below LLOQ will be treated as numerical zero.

Where data allow, the following PK parameters for AZD7648 will be derived from plasma concentrations:

Single dose Plasma PK Parameters (AZD7648 alone):

Core escalation monotherapy module, Part A, Cycle 0, Day 1

Combination escalation module, Part A, Cycle 0, Day 1

Cmax	Maximum observed plasma (peak) drug concentration
tmax	Time to reach peak or maximum observed concentration or response following drug administration
tlast	Time of last observed (quantifiable) concentration
AUC(0-12)	Area under the plasma concentration-time curve from time zero to 12 hours post-dose
AUC(0-24)	Area under the plasma concentration-time curve from time zero to 24 hours post-dose
AUClast	Area under the plasma concentration-curve from time zero to last quantifiable concentration
AUCinf	Area under plasma concentration-time curve from time zero to infinity
λz	Terminal elimination rate constant

t½λz	Half-life associated with terminal slope (λz) of a semi-logarithmic concentration-time curve, calculated as ln2/λz
CL/F	Apparent total body clearance of drug from plasma after extravascular administration
Vss/F	Volume of distribution (apparent) at steady state following extravascular administration
Vz/F	Volume of distribution (apparent) following extravascular administration (based on terminal phase)
MRTinf	Mean residence time of the unchanged drug in the systemic circulation
Dose normalised Cmax	Maximum observed plasma (peak) drug concentration divided by the dose administered (Cmax/D)
Dose normalised AUClast	Area under the plasma concentration-time curve from time zero to time of last quantifiable concentration divided by the dose administered (AUClast/D)
Dose normalised AUCinf	Area under the plasma concentration-time curve from time zero to infinity divided by the dose administered (AUCinf/D)
Dose normalised AUC(0-12)	Area under the plasma concentration-time curve from time zero to 12 hours post dose divided by the dose administered (AUC(0-12)/D))
Single dose Plasma PK Parameters (AZD7648 in combination with anti-cancer drug PLD): Combination escalation module, Part A, Cycle 1, Day 1	
Cmax	Maximum observed plasma (peak) drug concentration
tmax	Time to reach peak or maximum observed concentration or response following drug administration
tlast	Time of last observed (quantifiable) concentration
AUC(0-12)	Area under the plasma concentration-time curve from time zero to 12 hours post-dose
AUClast	Area under the plasma concentration-curve from time zero to last quantifiable concentration
Dose normalised Cmax	Maximum observed plasma (peak) drug concentration divided by the dose administered (Cmax/D)

Dose normalised AUClast	Area under the plasma concentration-time curve from time zero to time of last quantifiable concentration divided by the dose administered (AUClast/D)
Dose normalised AUCinf	Area under the plasma concentration-time curve from time zero to infinity divided by the dose administered (AUCinf/D)
Dose normalised AUC(0-12)	Area under the plasma concentration-time curve from time zero to 12 hours post dose divided by the dose administered (AUC(0-12)/D))

Multiple dose Plasma PK parameters (AZD7648 alone):
Core escalation monotherapy module, Part A, Cycle 1 Day 8 or Visit Y
AZD7648 in combination with anti-cancer drug:
Combination escalation module, Part A, Cycle 1, Day 8

Cmax	Maximum observed plasma (peak) drug concentration
tmax	Time to reach peak or maximum observed concentration or response following drug administration
tlast	Time of last observed (quantifiable) concentration
Cavg	Average drug concentration over a dosing interval
Ctrough	Lowest observed plasma (trough) drug concentration reached before the next dose is administered
AUCτ	Area under the plasma concentration-time curve in the dosing interval τ (τ = CCI and τ = CCI)
AUClast	Area under the plasma concentration-curve from time zero to last quantifiable concentration
CL/F	Apparent total body clearance of drug from plasma at steady state after extravascular administration
Dose normalised Cmax	Maximum observed plasma (peak) drug concentration divided by the dose administered (Cmax/D)
Dose normalised Ctrough	Minimum observed plasma concentration divided by the dose administered (Ctrough/D)

Dose normalised AUClast	Area under the plasma concentration-time curve from time zero to time of last quantifiable analyte concentration divided by the dose administered (AUClast/D)
Dose normalised AUCτ	Area under plasma concentration-time curve in the dosing interval τ divided by the dose administered (AUCτ/D)
Rac AUC	Accumulation ratio for AUC, calculated by multiple dose AUCτ/single dose AUC(0-12) (for CCI) or AUC(0-24) for CCI
Rac Cmax	Accumulation ratio for Cmax, calculated by multiple dose Cmax/single dose Cmax
TCP	Temporal change parameter in systemic exposure, calculated as multiple dose AUCτ/single dose AUCinf
Single dose Plasma Diagnostic PK Parameters (AZD7648 alone): **Core escalation monotherapy module, Part A, Cycle 0, Day 1** **AZD7648 in combination with anti-cancer drug:** **Combination escalation module, Part A, Cycle 0, Day 1**	
λz lower	Lower (earlier) t used for λz determination
λz upper	Upper (later) t used for λz determination
λzN	Number of data points used for λz determination
λz span ratio	Time period over which λz was determined as ratio of t½λz
Rsq adj	Statistical measure of fit for the regression used for λz determination adjusted for the number of used data points (λzN)
AUCextr	Extrapolated area under the curve from tlast to infinity, expressed as percentage of AUCinf

Urine PK Parameters

Where data allow, the following parameters will be calculated for AZD7648 from the urine concentration data obtained from the Core escalation monotherapy module Part A on Cycle 0 Day 1 (CCI cohorts) and Cycle 1 Day 8 (CCI):

Ae(t1-t2)	Amount of unchanged drug excreted into urine from time t1 to time t2, e.g. Ae(0-8) for Cycle 0 Day 1 and Cycle 1 Day 8 (CCI cohorts), Ae(8-24) for Cycle 0 Day 1 (CCI) and Cycle 1 Day 8 (CCI), and Ae(0-24) for Cycle 0 Day 1 (CCI) and Cycle 1 Day 8 (CCI)
fe(t1-t2)	Percentage of dose excreted unchanged in urine from time t1 to time t2, e.g. fe(0-8) for Cycle 0 Day 1 and Cycle 1 Day 8 (CCI cohorts), fe(8-24) for Cycle 0 Day 1 (CCI) and Cycle 1 Day 8 (CCI), and fe(0-24) for Cycle 0 Day 1 (CCI) and Cycle 1 Day 8 (CCI)
CLR	Renal clearance of drug from plasma estimated by dividing Ae(0-24) by AUC(0-24) for Cycle 0 Day 1 (CCI) and Cycle 1 Day 8 (CCI)

Additional PK parameters may be determined where appropriate (e.g. AUC(0-10/D) and AUC((0-24)/D).

There will be no PK parameters determined by the PK NCA methodology for the anti-cancer agents administered in this study e.g. PLD, since only sparse PK samples were planned for collection. The concentrations for the co-administered therapies will be listed and summarised, but any PK analysis carried out on the concentrations using other methods will be reported outside the CSR for this study.

3.2.2.3 CCI

The exploratory research variables are described in Section 3 of the Clinical Study Protocol.

CCI

4 ANALYSIS METHODS

4.1 General principles

The below mentioned general principles will be followed throughout the study:

- The planned arm and the actual arm for each patient will be assessed by study medical monitor and provided in a separate MS Excel sheet, which will be used for study summaries. This Excel file will be filed in the TMF at the end of the study.
- Unscheduled assessments will not be included in aggregate summaries and will be listed only. The assessments which are not included in the aggregate summary will be flagged in the listing. Unscheduled assessments will be included in the patient level figures.
- Descriptive statistics will be used for all variables, as appropriate. Continuous variables will be summarised by the number of observations, mean, standard deviation, median, upper and lower quartiles (as applicable), minimum, and maximum. For log transformed data it is more appropriate to present geometric mean, coefficient of variation (CV), median, minimum and maximum. Categorical variables will be summarised by frequency counts and percentages for each category.
- Descriptive statistics will only be presented if $n \geq 3$. If no patients have data at a given time point, then only $n = 0$ will be presented. If data are available for less than 3 participants, 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 modules (core, combination 1 module)/ parts (Part A: dose escalation, Part B: expansion cohorts)/doses.
- 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.

- SAS® 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.
- All analyses will be performed on data collected before intra-patient dose escalation, if any. Data collected after dose escalation will be presented in listings only and will be flagged. The actual dose at the time of the assessment will be presented in the listings.
- Additional sensitivity analysis might be performed on a subset of patients without important protocol deviations if needed.

4.2 Description of Analysis methods

In general, summaries will be split by modules/parts/Cohorts an doses.

4.2.1 Demographic, Dosing, and Safety and Tolerability data

There is no formal statistical analysis of safety and tolerability data required for this study. Demographic and other baseline disease characteristics, important protocol deviations, concomitant medication, dosing, exposure, safety, tolerability and DLT data will be listed and tabulated and summarised as defined by the current AZ standards (Oncology early phase study outputs).

Exposure

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

Actual and total treatment duration will be summarised by the following: mean, standard deviation, minimum, maximum, median and number of observations. In addition, the number and percentage of patients with at least one dose interruption and at least one dose reduction will be presented separately for the initial period of evaluability defined as 28 days and for any time following this initial period of the study. The number of treatment cycles received by patients will be summarised.

Exposure plots will be produced, with a line presented for each patient in the study. Dose intensity data will be summarised using medians, and quartiles as well as the minimum and maximum values.

Safety

Data from all cycles of initial treatment will be combined in the presentation of safety data.

An overall summary table of the number of patients experiencing each category of adverse event will be produced.

The number of patients experiencing treatment emergent adverse events by MedDRA system organ class (SOC) and MedDRA preferred term (PT) will be presented, with further splits by CTCAE grade, causal relationship to study medication and adverse events classed as Grade 3 or higher.

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

Any AE occurring within the defined 28 days follow-up period after discontinuation of investigational product will be included in the AE summaries. Any adverse events in this period that occur after a patient has received further therapy for cancer (following discontinuation of investigational product) will be flagged in the data listings. TEAEs occurring prior to first dose of investigational product (ie, before study Day 1) which subsequently worsen in severity following dosing will be presented in the summary tables. All other AEs occurring prior to first dose of investigational product (ie, before study Day 1), or after the 28 days follow-up period after discontinuation of investigational product will be listed separately, but not included in the summaries.

Fluctuations observed in CTCAE grades during study will be listed (where collected). When assigning a maximum CTCAE grade to a TEAE, only grade changes occurring after the date of first dose of study treatment and up to 28 days after the last dose of study treatment will be considered.

Details of any deaths will be listed for all patients.

Haematology and clinical chemistry results will be summarised using descriptive statistics (mean, median, standard deviation, minimum, maximum and number of observations). For all laboratory variables included in the current version of CTCAE, the CTCAE grade will be summarised. The post-baseline results and it's change from baseline for laboratory, ECG, vital signs data at each timepoint will be summarised. For all haematology and clinical chemistry results, change from baseline will be plotted using a spaghetti plot. Creatinine clearance and echocardiogram (LVEF) results at different timepoints and their change from baseline will be summarised using descriptive statistics. Creatinine clearance and echocardiogram (LVEF) results will be listed as well by visit. LVEF will also be summarised by categories listed in section 3.2.1.12. All abnormal findings from the physical exam will be listed. The number of patients for each ECOG-PS grade will be presented.

For the core module, individual 4β-hydroxy cholesterol concentration data will be listed only.

4.2.2 Tumour Response

Details of tumour 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, etc.

Best objective response and objective response rate (based on RECIST) will be summarised. For each module/part/cohort/dose, best objective response (BoR) will be summarised by n (%) for each category (CR, PR, SD, PD and NE). The best objective response table will be produced for (a) measurable disease and (b) measurable and non-measurable disease. Clopper-Pearson 80% confidence intervals for the ORR will also be presented in the table.

Target lesion size at each tumour assessment time point will be summarised for the evaluable for objective response set, along with percentage change from baseline (imputation will not be used for this) Also, the best percentage change in tumour size from baseline over all tumour assessment time points will be summarised for the evaluable for objective response set using descriptive statistics (n, mean, standard deviation, median, minimum, maximum).

Waterfall plots indicating the best percentage change from baseline in sum of the diameters of target lesions will be produced for the evaluable for objective response set. The plot will present each patient's best percentage change from baseline in TL tumour 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 tumour size level, which corresponds with the definition of 'partial' response and another reference line at +20%, corresponds with the definition of 'progressive disease' will be added to the plots. All progressions will be marked with a '●' or designated with patterns or colours for ORR categories. Flagged progressions on the percentage change in TL tumour size at a particular timepoint will be based upon NTL or new lesion progression at that timepoint and flagged progressions on the best percentage change will be based upon NTL or new lesion progression at the same timepoint as the best percentage change. 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 will be 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 will be produced for each treatment group for the evaluable for objective response set. Separate plots should be presented for the absolute value in the sum of target lesions and percentage change in target lesion size over time. These plots depict the sum of target lesion size for each patient or each patient's percentage change in TL tumour 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.). The scale on y-axis for percentage change plots will be fixed from -100 to +100 to avoid presenting extreme values.

If there are sufficient data, Kaplan Meier plots of DoR will be presented for (a) the evaluable for objective response set; (b) the evaluable for efficacy set. If there are sufficient data, median DoR will also be summarised calculated from the KM curve for both sets. Only patients who have a confirmed response will be included in this summary table. Swimmer plots that clearly show the profile of each patient who responds will be produced for both sets.

Progression-free survival (PFS) will be summarised using Kaplan-Meier methodology for the evaluable for efficacy set. If there are sufficient data, median time to event, and quartiles will be summarised, including 80% CI. The percentage of patients progression free every 3 months (e.g. at 3, 6, 9, 12, 15 months), along with the 80% CI will also be presented. Kaplan Meier curves will be plotted.

4.2.3 Pharmacokinetics data

The plasma concentrations of AZD7648 and PLD, and the PK parameters of AZD7648 will be presented in the tables, figures and listings in accordance with the of the AstraZeneca Corporate CSRHLD Reporting standards version 3.4, that include applicable descriptive statistics for the PK tables and figures, information for handling of individual concentrations below the LLOQ for the descriptive statistics and figures, and precision and rounding rules for PK concentration and parameter data in the listings and summary tables.

Any patients to be excluded from the pharmacokinetics set set, or individual PK concentration or parameter data values to be excluded from the summary tables and figures, will be discussed and agreed between the PK scientist with the AZ Clinical Pharmacology Scientist at the time of database lock when all information that may impact the integrity of the PK data is available. Any exclusions will be provided to programming in the PK handover document and flagging file in accordance with AZ global functional guideline for PK evaluations, together with justification for the exclusion and will be clearly documented in the TFLs and CSR. These individual data will still be presented in the listings, but will be flagged and footnoted with explanatory text to identify that they are excluded from summary outputs.

Plasma Concentration Data

A listing of concentration versus scheduled time data will be presented for each module, study part, cohort, dose regimen, and Cycle/PK day for each analyte for all patients in the safety set. PK concentration data listings will be presented to the same number of significant figures as the data received from the bioanalytical laboratory (usually but not always to 3 significant figures) and against the same units as received.

The plasma concentrations of AZD7648 and PLD for each scheduled time point will be summarised by module, study part, cohort (dosing regimen), and Cycle/PK day (single dose or multiple dose) based on the pharmacokinetics set.

The PK plasma concentration data will be summarised using the following descriptive statistics:

n, n < lower limit of quantification (LLOQ), arithmetic mean (mean), arithmetic standard deviation (SD), geometric mean (gmean), gmean -/+ geometric SD (gmean –gSD and gmean + gSD), geometric coefficient of variance % (gCV%), median, minimum (min) , maximum (max).PK concentration descriptive statistics will all be presented to 4 significant figures with the exception of the min and max which will be presented to 3 significant figures and n and n <LLOQ which will be presented as integers.

Combined individual plasma concentration versus actual elapsed times will be plotted on both the linear and semi-logarithmic scale for the pharmacokinetics set and the plots will be grouped by module, study part, cohort (dosing regimen), and Cycle/PK day.

Plots showing geometric mean (-/+ gSD) plasma concentrations versus nominal time will be presented separately for each module, study part and Cycle/PK day showing all cohorts (dose regimens) on the same plot, on both linear and semi logarithmic scale for the pharmacokinetics set. Additional geometric mean plots may also be presented separately for each module, study part and cohort (dosing regimen) showing all Cycle/PK days on the same plot, on both linear and semi logarithmic scale for the pharmacokinetics set.

The following rules will be followed with regards to the handling of individual concentrations below the lower limit of quantification (LLOQ) of the bioanalytic assay:

Individual concentrations below the LLOQ will be reported as NQ (non-quantifiable) in the listings with the LLOQ defined in the footnotes of the relevant TFLs. Individual plasma concentrations that are Not Reportable will be reported as NR and those that are missing will be reported as NS (No Sample) in the

listings. Plasma concentrations that are NQ, NR or NS will be handled as follows for the provision of descriptive statistics:

- Any values reported as NR or NS will be excluded from the summary tables and corresponding figures.
- At a time point where less than or equal to 50% of the values are NQ, all NQ values will be set to the LLOQ, and all descriptive statistics will be calculated.
- At a time point where more than half of the values are NQ, gmean, gmean-gSD, gmean+gSD and gCV% will be set to NC [Not Calculated]). The maximum value will be reported from the individual data, and the minimum and median will be set to NQ.
- If all values are NQ at a time point, no descriptive statistics will be calculated for that time point. The gmean, mean, min, median and max will be reported as NQ and gmean -/+SD, gCV% and gSD as NC.
- The number of values below LLOQ (n < LLOQ) will be reported for each time point together with the total number of collected values (n).

Three observations > LLOQ are required as a minimum for a plasma concentration to be summarised. Two observations > LLOQ are presented as minimum and maximum with the other summary statistics as NC. One observation > LLOQ is presented as maximum with other summary statistics as NC.

For mean figures, concentrations that are NQ will be handled as described for the descriptive statistics.

Single dose studies: For individual figures, concentrations that are NQ will be regarded as missing, with the exception of pre-dose NQ values which will be set to 0 for linear scale plots.

Multiple dose studies: For individual figures, concentrations that are NQ will be regarding as missing, with the exception of pre-dose NQ values on Day 1 of dosing, which will be set to 0 for linear scale plots.

Urine Concentration Data

Urine concentration of AZD7648 and volume/weight data will be listed by collection interval. The listing will include protocol scheduled sampling interval, and sample collection start and stop times and will be presented for all patients in the safety set.

Plasma and urine Parameters Data

All reportable plasma and urine AZD7648 PK parameters, including individual plasma diagnostic and λz related parameters, will be listed for each module, study part, cohort (dosing regimen), and Cycle/PK day for all patients in the safety set.

All plasma and urine PK parameters for AZD7648 will be summarised by module, study part, cohort (dosing regimen) and Cycle/PK day using appropriate descriptive statistics, based on the pharmacokinetics set.

The PK parameters will all be presented to 3 significant figures with the exception of:

- Cmax and Ctrough which will be presented to the same number of significant figures as received from the bioanalytical laboratory
- tmax, tlast, λz lower and λz upper which will be presented as actual time received in the data, usually to 2 decimal places
- n and λzN which will be presented as an integer (no decimals)

The following descriptive statistics will be presented for all plasma and urine PK parameters:

n, arithmetic mean, SD, gmean, gmean - gSD, gmean + gSD, gCV%, median, min and max.

with the exception of the following:

- tmax and tlast will be presented as n, median, minimum and maximum.

The descriptive statistics for all PK parameters will be presented to 4 significant figures, with the exception of min and max will be presented to 3 significant figures and n which will be presented as an integer, apart from for the following parameters:

- tmax,, tlast, λz lower and λz upper which will be presented as received in the data, usually to 2 decimal places.

4.2.4 Pharmacodynamics

Pharmacodynamics exploratory analyses will be described in a separate document.

4.2.5 Exploratory research variables

PK, PDc, and biomarker research and pharmacogenetics exploratory analyses will be described in a separate document. The population PK analysis and PDc analyses will be presented separately from the main CSR.

5 INTERIM ANALYSES

Interim analysis is not applicable.

6 CHANGES OF ANALYSIS FROM PROTOCOL

Some of the PK parameter symbols specified in CSP objective and endpoints been re-defined in SAP section 3.2.2.2 to match with AZ Corporate CSRHLD Reporting Standards version 3.4 (see Table 10)

Table 10: PK parameter symbols re-defined in SAP

Table 10: PK parameter symbols re-defined in SAP

Protocol defined PK symbols	Symbols re-defined in SAP	Parameter definition
AUC	AUCinf	Area under plasma concentration-time curve from zero to infinity (Part A)
AUCtau	AUCτ	Area under plasma concentration-time curve in the dosing interval τ (τ = 24 for CCI dose and τ =12 for CCI dose)
AUC0-t	AUClast	Area under the plasma concentration-curve from zero to the last quantifiable concentration
Cmax,ss	Cmax	Maximum observed plasma (peak) drug concentration after multiple dose
Cmin,ss	Cmin	Minimum observed plasma concentration after multiple dose
Half-life	t½λz	Half-life associated with terminal slope (λz) of a semi-logarithmic concentration-time curve, calculated as ln2/lz
t½	t½λz	Half-life associated with terminal slope (λz) of a semi-logarithmic concentration-time curve, calculated as ln2/lz

Additional PK plasma and urine parameters of interest are elaborated in section 3.2.2.2 of SAP.

7 REFERENCES

1. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer 45 (2009) 228 – 247.

2. RECIST 1.1 – Update and Clarification: From the RECIST Committee. Eur J Cancer. 2016 Jul; 62: 132–137. 3. Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated

3. SAS Institute Inc. 2013. SAS® 9.4 Statements: Reference. Cary, NC: SAS Institute Inc.

4. The SAS System Requirements for SAS® 9.4 Foundation for Microsoft Windows: Copyright ©2020. SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.

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