Title: A Modular Phase 2a Multicentre Open-Label Study to Investigate DNA-damage Response Agents (or Combinations) in Patients With Advanced Cancer Whose Tumours Contain Molecular Alterations (PLANETTE)

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AstraZeneca AB

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A Modular Phase 2a Multicentre Open-Label Study to Investigate DNA-damage Response Agents (or Combinations) in Participants With Advanced Cancer Whose Tumours Contain Molecular Alterations (PLANETTE)

Statistical Analysis Plan

Version: 3.0

Parexel Project Number: 247947

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REVISION HISTORY

Version No.	Effective Date	Summary of Change(s)
Final v1.0	23 Mar 2021	New Document
Version 2.0	16 Sep 2021	General changes Replaced all 'patients' to 'participant' to match the language with CSP v 2.0 PSA decline ≥ 50% is replaced with PSA decline > 50% wherever appropriate. Section 1.0 Updated the protocol amendment with latest version and date Updated the CRF with latest version and date. Section 2.1.1 Cohort A objective and endpoints table. Removed the endpoints - electrocardiogram, urinalysis and coagulation parameters from secondary objective to assess the safety and tolerability profile of ceralasertib. CCI [redacted] Section 2.1.2 Cohort B objective and endpoints table Revised the primary objective to read as follows: To obtain a preliminary assessment of the efficacy of ceralasertib in participants with ATM altered metastatic castration-resistant prostate cancer as assessed by composite response rate. Corrected the secondary efficacy objective to read as follows: • Proportion of participants with confirmed PSA decline > 50%. • Best percentage change in the tumour size. Removed the endpoints - electrocardiogram, urinalysis and coagulation parameters from secondary objective to assess the safety and tolerability profile of ceralasertib. CCI [redacted] CCI [redacted]

		CCI [redacted] CCI [redacted] Section 3.1.1 Updated the with changes made to the study design during protocol amendment 2.0 Added the change in starting dose of ceralasertib in the study during protocol amendment 2.0 The starting dose was reduced from 240 mg BID, Day 1 to Day 1 to 160 mg BID , Day 1 to Day 14, of every 28-day cycle. Added the brief overview of the study population (number of patients dosed on 240 mg ceralasertib) in each cohort at the time of protocol amendment 2.0. Intention to enroll additional participants into cohort A and Cohort B at the 160 mg BID to match the required sample size is also added. Figure 1 - Study design of Cohort A is updated as per protocol amendment. Figure 2 - study design of Cohort B is updated as per protocol amendment 2.0 Section 3.2 Table : summary of analysis during study conduct The trigger/timepoint for interim and final analyses of cohort A and B are updated. Sample size requirement for each analysis specified in protocol should match with population size in 160 mg BID starting dose for each cohort to trigger the analyses. Section 4.2 The general presentation considerations are updated to read as follows: All summaries, figures and listings for all non-comparative cohorts will be provided separately for each module. Demographic and baseline characteristics of the participants in each module will be summarised by cohort and by starting dose of ceralasertib. All safety data and PK data will be summarised by cohort, by starting dose of ceralasertib and timepoint. All

		efficacy data will be summarised only for participants who received ceralasertib 160 mg BID as starting dose by cohort. Section 4.3.2 visit windowing Table 2: Visit windowing for vital signs and laboratory values is completely revised. Section 4.6.2 Protocol deviations Added a general statement as follows to accommodate all potential revisions to protocol deviation specification during the study period. 'All IPDs as per the latest PD specifications, not limited to the following will be summarised and listed separately for each module, by cohort and by starting dose of ceralasertib'. Section 4.6.3 Updated how the summaries and listings for module1, demography and baseline characteristics will be presented. Section 4.7 Updated how the summaries and listings for module 1, medical and surgical history will be presented. Section 4.16.1 Added a new section to explain the population for efficacy endpoints summaries and listings. Only participants in 160 mg BID starting dose will be used for efficacy summaries. All participants' information will be listed. Section 14.17.3 PFS (Cohort A) and 14.17.8 rPFS (cohort B) An additional time point - three months, added to assess the proportion of participants alive and progression free. Section 4.20 Updated how the summaries and listings will be presented for module 1, PK concentration data will be presented.
Version 3.0	30Jan2023	Updated protocol version to 3.0 Date: 04 April 2022 Updated eCRF version to 7.0 Date: 14 Jul 2022 Corrected spelling of investigational product from 'ceralacertib' to 'ceralasertib'.

		Section 1.1.1 Deletion of text “ensuring at least 60% of participants with ATM IHC ≤ 5%” Replaced Figure 1 and updated the footnotes to match CSP 3 Cohort B Replaced Figure 2 and updated footnotesto match CSP3 Section 3.2 Interim Cohort A Deletion of text “ensuring at least 60% of participants with ATM IHC ≤ 5%” Interim Cohort B Deletion of text “ensuring at least 60% of participants with ATM IHC ≤ 5%” Section 4.2 Revised the general presentation guidelines for treatment group by assigned starting dose rather than starting dose. Section 4.8 Updated the language to specify that allowed and disallowed concomitant medications those are ongoing or starting on or after the first dose of study treatment and up to the date of last dose of study treatment will be summarized. Section 4.15 Added ATM mutation subcategories and CCI [redacted] CCI [redacted] to the subgroup analysis. Section 4.17.2 Added the paragraph to explain how percentage change from baseline in target lesions waterfall plot will be plotted for ATM mutation/CCI [redacted] subcategories. Section 4.17.3 Added ‘time to progression’ swimmer plot. Section 4.19.1.1 Updated the section with conditions to accommodate the 14 days on and 14 days off dosing schedule Section 4.19.1.2

		Updated with more details for RDI calculation. Section 4.19.2 Updated the language to specify that only AEs with an onset or that worsen on or after the date of first dose and up to and including 30 days after the date of last dose of IP will be summarized. Updated the language to include additional AE tables by ATM gene variant status, by preferred term. Section 4.19.7 Updated with 'Not applicable' Table 4 Added new analysis set 'interim analysis set' Table 5, Table 6 Added new analysis set 'interim analysis set' is added to all efficacy end point.

LIST OF ABBREVIATIONS

Abbreviation / Acronym	Definition / Expansion
AEs	adverse events
AESIs	adverse events of special interests
ARID1A	AT-Rich Interaction Domain 1A
AST	advanced solid tumour
ATC	anatomical therapeutic chemical
ATM	ataxia telangiectasia mutated
AZ	AstraZeneca
BICR	blinded independent central review
BID	twice daily
BLoQ	below the limit of quantification
BMI	body mass index
CI	confidence interval
cm	centimeter
CR	complete response
CSP	clinical study protocol
CSR	clinical study report
CT	computed tomography
CTC	circulating tumour cells
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DCO	data cut off
DNA	deoxyribonucleic acid
DDR	damage response agents
DoR	date of response
ECG	electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	electronic Case Report Form
IHC	immunohistochemistry
kg	kilogram
KM	Kaplan-Meier
LD	longest diameter
LLoQ	lower Limit of quantification
mCRPC	metastatic Castration-Resistant Prostate Cancer
MedDRA	Medical Dictionary for Regulatory Activities
mL	milliliter
MRI	magnetic resonance imaging
NA	not applicable

NC	not calculable
NE	not evaluable
NHA	novel hormone agent
NQ	not quantifiable
NR	not reportable
NS	no sample
NSCLC	non-small-cell lung carcinoma
NTL	non-Target Lesions
OAEs	other significant adverse events
ORR	objective response rate
OS	overall survival
PCWG3	Prostate Cancer Working Group 3
PD	progressive disease
PDc	pharmacodynamics
PFS	progression free survival
PK	pharmacokinetic
PR	partial response
PSA	prostate specific antigen
PT	preferred term
PXL	PAREXEL®
RECIST 1.1	Response Evaluation Criteria in Solid Tumours 1.1
rORR	radiological objective response rate
SAEs	serious adverse events
SAP	statistical analysis plan
SD	Stable Disease
SOC	system organ class
StD	standard deviation
TEAEs	treatment emergent adverse events
TL	target lesions
WHODD	World Health Organization Drug Dictionary

1 INTRODUCTION

This is a modular, phase 2a, open-label, multicentre study to investigate deoxyribonucleic acid (DNA) – damage response (DDR) agents or combinations in participants with advanced cancers (advanced/metastatic solid and/or haematological malignancies with molecular alterations) whose tumours contain molecular alterations which may include, but not limited to, ataxia telangiectasia mutated (ATM) and AT-Rich Interaction Domain 1A (ARID1A), and relevant tumour indications may be confined to a single tumour type or a collection of specific tumour types or disease agnostic.

The core module provides the overall framework for the entire study. The participant population and the molecular alterations required for each module will be provided separately as it is added to the study.

The Module 1 will be investigating ceralasertib monotherapy administered orally to participants with advanced/metastatic solid malignancies with ATM mutation and/or protein loss. Additional modules or cohorts may be added to the study after submitting available supporting data for that module/cohort and after substantial protocol amendment.

The scope of this statistical analysis plan (SAP) is to describe in detail the technical elaboration of statistical analysis of the efficacy, safety and tolerability of ceralasertib in Module 1 as outlined in clinical study protocol (CSP).

The analysis described in this SAP are based on the following documents:

- Clinical Study Protocol, Version Amendment 3.0 (04 April 2022).
- electronic Case Report Form (eCRF), Version 7.0 (14 Jul 2022).
- The specifications for tables, listings and figures are contained in a separatedocument.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Module 1

2.1.1 Cohort A: Advanced Solid Tumour (AST)

Objectives	Endpoints/Variables
Primary	
To obtain a preliminary assessment of the efficacy of ceralasertib in participants with ATM altered AST refractory to standard treatments options, as assessed by objective response rate (ORR).	Investigator assessed ORR, as defined by Response Evaluation Criteria in Solid Tumours (RECIST) 1.1[1,2].
Secondary	
To further assess the efficacy of ceralasertib.	Investigator assessment, as defined by RECIST 1.1: • Duration of Response (DoR)

	• Percentage change in tumour size • Progression free survival (PFS)
To assess the safety and tolerability profile of ceralasertib.	Adverse events (AEs)/ Serious AEs (SAEs) • Vital signs • Haematology • Clinical chemistry parameters
Exploratory	
CCI	• CCI • CCI
CCI	• CCI • CCI
CCI	

2.1.2 Cohort B: metastatic Castration-Resistant Prostate Cancer (mCRPC)

Objectives	Endpoints/Variables
Primary	
To obtain a preliminary assessment of the efficacy of ceralasertib in participants with ATM altered metastatic castration-resistant prostate cancer as assessed by composite response rate.	Composite response rate (investigator assessed radiological response by RECIST 1.1 for soft tissue and visceral lesions and by Prostate Cancer Working Group3 [PCWG3[3]] criteria for bone lesions, Prostate Specific Antigen [PSA] decline, and/or Circulating tumour Cell [CTC] conversion).
Secondary	
To further assess the efficacy of ceralasertib	• ORR by RECIST 1.1 for soft tissue and visceral lesions and by PCWG3 criteria for bone metastases.

	• Proportion of participants with confirmed CTC count conversion from unfavourable to favourable. • Proportion of participants with confirmed PSA decline > 50%. • Best percentage change in the tumour size. • Duration of radiological response. • Radiological PFS (rPFS) using RECIST 1.1 for soft tissues and visceral lesions and PCWG3 for bone lesions.
To assess the safety and tolerability profile of ceralasertib	• AEs/SAEs • Vital signs • Haematology • Clinical chemistry parameters
Exploratory	
CCI [redacted]	• CCI [redacted]. • CCI [redacted] • CCI [redacted] • CCI [redacted] • CCI [redacted] • CCI [redacted] • CCI [redacted] • CCI [redacted] • CCI [redacted]. • CCI [redacted]

CCI

CCI

- CCI
- CCI
- CCI
- CCI

[a] CCI

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design

3.1.1 Module 1

Module 1 is investigating ceralasertib monotherapy, previously known as AZD6738, administered orally twice daily (BID), to participants with AST with ATM mutation and/or protein loss.

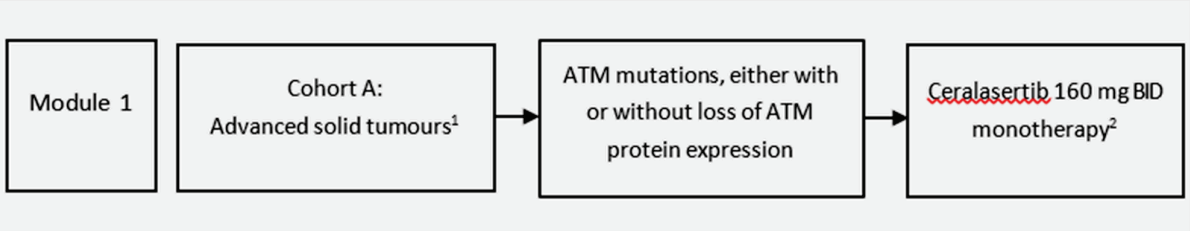
Originally, a higher starting dose of ceralasertib was selected for this study, at 240 mg BID, Day 1 to Day 14, of every 28-day cycle. At the time of protocol amendment 2, it was decided to reduce the starting dose of ceralasertib to 160 mg BID Day 1 to Day 14, in a 28-day cycle.

At the time of protocol amendment 2, 8 participants had been dosed at 240 mg BID in Cohort A, and 1 participant had been dosed at 240 mg BID in Cohort B. Following the reduction of the starting dose from 240 mg BID to 160 mg BID in protocol amendment 2, the intention is to enroll an additional total of ~25 and ~27 participants in Cohort A and B, respectively, at the 160 mg BID.

Cohort A is recruiting participants with ATM altered AST, except participants with non-small-cell lung carcinoma (NSCLC) and prostate cancer. Restrictions may be introduced on tumour types with low ATM mutation prevalence and to ensure a balanced number of tumour types. Approximately 25 molecularly eligible and centrally confirmed participants will be enrolled into Cohort A. Cohort A may be further expanded, CCI. This would occur in the event of an efficacy signal is observed, and subject to a protocol amendment. Refer to Figure 1 for Module 1 Cohort A study design.

Figure 1: Study design - Cohort A

Protocol amendment 3

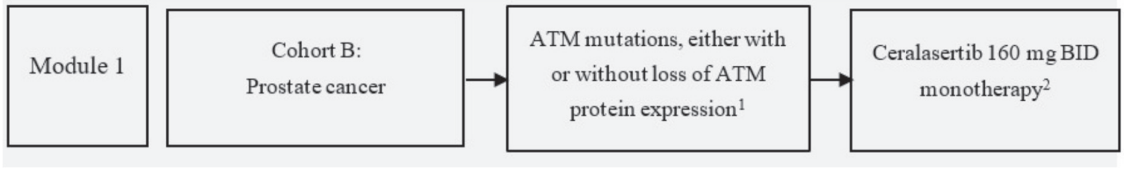


[1]All aST, excluding participants with NSCLC and prostate cancer.
[2]Ceralasertib administered twice a day between Days 1 to 14 in 28 day cycles.
Abbreviations: ATM=ataxia telangiectasia mutated; BID=twice daily; IHC=immunohistochemistry; NSCLC=non-small-cell lung carcinoma.

Cohort B is recruiting participants with ATM altered mCRPC (metastatic castration-resistant prostate cancer). Approximately 27 molecularly eligible and centrally confirmed participants will be enrolled into Cohort B. Unfavourable CTC count requirement may be introduced for all participants to ensure adequate (approximately ≥ 50%) number of participants with CTC count ≥ 5/7.5 mL blood. Cohort B may be further expanded, CCI [redacted]. This would occur in the event an efficacy signal is observed, and subject to a protocol amendment. Refer to Figure 2 for Module 1 Cohort B study design.

Figure 2: Study design - Cohort B

Protocol amendment 3



[1] Unfavourable CTC count requirement may be introduced for all participants to ensure adequate (approximately ≥ 50%) number of participants with CTC count ≥ 5/7.5 mL blood. ATM 'deficient' is defined as ATM IHC ≤ 5% ATM-positive tumour nuclei using the Ventana assay (VENTANA ATM (Y170) RPA Assay).
[2] Ceralasertib administered twice a day between Days 1 to 14 in 28 day cycles.
Abbreviations: ATM=ataxia telangiectasia mutated; BID=twice daily; IHC=immunohistochemistry.

3.2 Planned Analyses for Module 1

All AstraZeneca (AZ) and Parexel (PXL) team members involved in this study will remain unblinded. The details of the analyses planned during the conduct of this study if outlined in Table 1.

Table 1: Summary of Analyses During study conduct

Analysis	Trigger/Timepoint	Data included

Interim Cohort A	Approximately 4 months after 18 molecularly eligible centrally confirmed evaluable for response participants (are enrolled in 160 mg BID starting dose.	Efficacy data specific to Cohort A Safety Data
Interim Cohort B	Approximately 6 months after 12 molecularly eligible centrally confirmed evaluable for response participants are enrolled in 160 mg BID stating dose.	Efficacy data specific to Cohort B Safety Data
Primary Analysis Cohort A	Approximately 6 months after 25 molecularly eligible centrally confirmed evaluable for response participants are enrolled in 160 mg BID stating dose.	All data for Cohort A
Primary Analysis Cohort B	Approximately 6 months after 27 molecularly eligible centrally confirmed evaluable for response participants are enrolled in 160 mg BID stating dose. .	All data for Cohort B

4 STATISTICAL METHODS

4.1 Data Quality Assurance

All tables, figures and data listings to be included in the report will be independently checked for consistency, integrity and in accordance with standard Parexel procedures.

4.2 General Presentation Considerations

All summaries, figures and listings for all non-comparative cohorts will be provided separately for each module.

Demographic and baseline characteristics of the participants in each module will be summarised by cohort and by assigned starting dose of ceralasertib. All safety data and PK data will also be summarised by cohort, by assigned starting dose of ceralasertib and timepoint. All efficacy data will be summarised only for participants who were assigned to ceralasertib 160 mg BID as starting dose by cohort.

Continuous data will be summarized using descriptive statistics (the number of participants [n], mean, standard deviation [StD], median, 25th and 75th percentiles [where appropriate], minimum and maximum unless otherwise stated). For logtransformed data it is more appropriate and will present geometric mean (gmean), geometric coefficient of variation (CV), median, minimum and maximum.

For continuous data, the mean, median and gmean will be rounded to one additional decimal place compared to the original data. The StD and geometric CV will be rounded to two additional decimal places compared to the original data. Minimum and maximum will be displayed with the same

accuracy as the original data. The maximum number of decimal places reported will be four for any summary statistic.

Categorical data will be summarized in terms of the number of participants providing data at the relevant time point (n), frequency counts and percentages. Percentages will not be presented for 0 (zero) counts. Unless otherwise stated, percentages will be calculated using the number of participants included in the analysis set for that treatment group as denominator and presented to one decimal place.

Confidence intervals (CIs) and p-values, when presented, will generally be constructed at the 2-sided alpha level specified for that module. For Module 1 a two-sided 80% CIs will be constructed and presented to one additional decimal place compared to the original data.

For assessments on the day of first dose where time is not captured, a nominal pre-dose indicator, if available, will serve as evidence that the assessment occurred prior to first dose. Assessments on the day of first dose where neither time nor a nominal pre-dose indicator are captured will be considered prior to first dose if such procedures are required by the protocol to be conducted before first dose.

For efficacy, safety endpoints, baseline will be the last non missing value obtained prior to the first dose/administration of study medication and any information taken after first dose/administration of study medication will be regarded as post baseline information. If two visits are equally eligible to assess participant status at baseline (e.g., screening and baseline assessments both on the same date prior to first dose/administration), 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 will be taken as baseline as this is the most conservative. Where safety data are summarised over time, study day will be calculated in relation to date of first treatment. If no value exists before the first dose/administration, then the baseline value will be treated as missing.

In all summaries:

Change from baseline = post-baseline value - baseline value.

Percent change from baseline=

$$\frac{\text{post-baseline value - baseline value}}{\text{baseline value}} \times 100.$$

For any variable subject to log transformation, the back transformed change from baseline, calculated and summarised on the log scale, will be presented as the ‘baseline scaled ratio’ (BSR). Percentage change will then be calculated as (BSR – 1) x 100.

4.3 General variables

4.3.1 Study Day definition

Study day 1 is defined as the date of first dose of study treatment.

For visits (or events) that occur on or after first dose of study treatment

Study day = Date of visit [event] – Date of first dose of study treatment + 1.

For visits (events) that occur prior to first dose

Study day = Date of visit [event] – Date of first dose of study treatment.

The reference date for all assessments (efficacy, safety, PK, etc.) is the start of the study treatment in Cycle 1. There is no study day 0 defined for this study.

For listings (such as AEs) that include the derivation "Days since last dose", defined as

Days since last dose = Event date – Date of last dose.

Where "Date of last dose" is defined as the date of dosing immediately preceding the event occurrence. Events that occur on the same day as the last dose of study treatment will therefore be described as occurring zero days from last dose of study treatment.

4.3.2 Visit windowing

Time windows will need defining for any presentations that summarise values by visit. The following conventions should apply:

- For summaries of post-baseline values by scheduled visits of all endpoints with the exception of the PK endpoints.
- The time windows will be exhaustive so that data recorded at any time point including unscheduled visits has the potential to be included in summaries.
- Inclusion within the time window will be based on the actual date and not the intended date of visit, according to the rules reported in.
- If there is more than one value per participant within a time window then the closest value to the intended visit date will be summarised, or the earlier, in the event the values are equidistant from the intended visit date. The listings will indicate which value for a participant contributed to the summary table, wherever feasible.
- Plasma PK samples collected outside of the specified window as in CSP will not have their concentrations included in the summary for that scheduled time-point.

Table 2: Visit Windowing for vital signs and laboratory values

Module 1

(C: Cycle; D: Day [C1D1: Cycle1 Day1])

eCRF visit	Target Day	Analysis visit window for Haematology and other lab safety values	Analysis visit window for Vitals and ECOG
Screening 1	N/A	N/A	N/A
Screening 2	-28 to -1	-28 to -1	-28 to -1
C1D1[b]	Day 1[a]	C1D1[a]	C1D1[a]

C1D8	Day 8	C1D1+7 (±1) days	C1D1+7 (-3/+2) days OR C1D5 to C1D10
C1D14	Day 14	C1D1+13 (±2) days	(C1D1+13) - 3 days to C2D1 - 2 days OR C1D11 to C2D1 - 2 days
C2D1[b]	Day 29	C2D1 - 1 day to C2D1	C2D1 - 1 day to C2D1 + 3 days (C2D4)
C2D8	Day 36	C2D1+7 (±1) days	C2D1+7 (-3/+2) days OR C2D5 to C2D10
C2D14	Day 42	C2D1+13 (±2) days	(C2D1+13) - 3 days to (C3D1 -2) days OR C2D11 to C3D1 - 2 days
CxD1[b],[c]	Day 1 + (x-1)*28 days	CxD1 -1 day to CxD1	CxD1 - 1 day to CxD1 + 3 days (CxD4)
IP DISC	-	IP Disc date +14 days	IP Disc date + 14 days
Safety follow-up	IP DISC + 30 (±7) days	IP Disc date + 14 days to IP Disc date + 37 days	IP Disc date + 14 days to IP Disc date + 37 days

[a] Any value up to Day 1 including pre-treatment time will be considered as baseline. The handling of duplicate baseline value will be explained in Section 4.2.
[b] The start date of dosing of each cycle (CxD1) should be taken from the exposure data.
[c] $X \geq 3$.
eCRF - electronic Case Report Form. IP DISC - Investigational Product discontinuation.

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 and if it was collected at a scheduled or unscheduled visit).

Listings will display all values contributing to a time point for a participant; they will also highlight the value for the participants that will be used in the summary table, wherever possible.

RECIST and bone lesion (for cohort B only) assessments for all participants will be assessed every 8 weeks (±7 days) after Cycle 1 day 1 for the first year and every 12 weeks (±7 days) thereafter until objective disease progression by RECIST 1.1 (for cohort A) or radiological progression (for cohort B). Analysis visit windows will be assigned to the RECIST (cohort A) / radiological (cohort B) overall visit response assessments so that all assessments are allocated to the nearest scheduled time point. If more than one assessment falls in a given visit window, then the value closest to the protocol scheduled time point will be used. In the event of an equidistant time point, the earlier time point will be used.

Table 3: RECIST/bone lesion Assessments Visit Windows

(W: Week)

Week Number	Days after first dose of the treatment (Cycle 1 Day 1)	Visit Window Label	Visit Window
8	57	W8	[Day 50; Day 84]
16	113	W16	[Day 85; Day 140]
24	169	W24	[Day 141; Day 196]
32	225	W32	[Day 197; Day 252]
40	281	W40	[Day 253; Day 308]
48	337	W48	[Day 309; Day 364]
56	393	W56	[Day 365; Day 434]
68	477	W68	[Day 435; Day 518]
80	561	W80	[Day 519; Day 602]
92	645	W92	[Day 603; Day 686]
104	729	W104	[Day 687; Day 770]
….	….	….	…..
Until RECIST 1.1 progression			

4.3.3 Handling Missing Data

In general, other than for the below described, or where otherwise specified in the particular analysis, missing data will not be imputed and will be treated as missing.

4.3.3.1 Imputation of Adverse event and Concomitant medication.

- Missing day: impute with the 1st of the month unless month and year are same as month and year of first dose of study treatment then impute with first dose date.
- Missing day and month: impute with 1st January unless year is the same as first dose date then impute with first dose date.
- Completely missing: impute with date of first dose of 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.

When imputing a start date ensure that the new imputed date is sensible i.e. is prior to the end date of the AE or medication.

4.3.3.2 Imputation of Adverse Event and concomitant medication end date.

- Missing day: impute with the last day of the month, unless month and year are the same as month and year of last dose of study treatment, then impute with the last treatment date in that month.

- Missing day and month: impute with 31st of December unless the year is the same as the year of last dose of the study treatment, then impute with the last treatment date of that year.
- Completely missing: assume the event is still ongoing and do not impute any date if it is flagged as "ongoing".

Generally, the imputation of dates is to decide if an observation is for AEs or concomitant for medications. Flags will be retained in the database indicating where any programmatic imputation has been applied, and in such cases, durations and study days will not be calculated.

4.3.3.3 Imputation for Laboratory Values Outside of Quantification Range

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 similarly.

4.4 Software

All report outputs will be produced using SAS®[4] version 9.4[5] or later in a secure and validated environment.

4.5 Analysis Data Sets

4.5.1 Module 1

Details of all analysis sets defined for Module 1 are presented in Table 4.

Table 4: Analysis set

Analysis set	Definition
Enrolled analysis set	All study participants who signed the informed consent form (including screening failures).
Evaluable for response set	Cohort A: All study participants with measurable baseline disease who received at least 1 dose of study intervention. Cohort B: All study participants with measurable disease and/or unfavourable CTC count at baseline who received at least 1 dose of study intervention.
[a]Molecularly eligible centrally confirmed set	All molecularly eligible and centrally confirmed participants who received at least 1 dose of study intervention.

[a]Molecularly eligible centrally confirmed evaluable for response set	Cohort A: All molecularly eligible and centrally confirmed study participants with measurable baseline disease who received at least 1 dose of study intervention. Cohort B: All molecularly eligible and centrally confirmed study participants with measurable disease and/or unfavourable CTC count at baseline who receive at least 1 dose of study intervention.
CCI [redacted]	CCI [redacted]
CCI [redacted]	CCI [redacted]
Safety set	All participants who received at least 1 dose of study intervention.
Interim analysis set	All participants in the molecular eligible centrally confirmed evaluable for response set with a chance to have at least two follow up RECIST assessments (i.e. all patients who received first dose of ceralasertib, at least 16 weeks prior to the data cut off date).

[a] Please refer to the latest CSP for more details regarding central confirmation. A separate specification document will be provided to support the programming of the 'centrally confirmed' flag.

Upon database release, protocol deviation and analysis set outputs will be produced and will be sent to AZ for review. Prior to database lock, analysis set classification meeting will be arranged to discuss the outputs and decide which participants and/or participant data will be excluded from certain analyses. Decisions made regarding the exclusion of participants and/or participant 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 5 (Cohort A) and Table 6 (Cohort B).

Table 5: Summary of outcome variables and analysis sets for Cohort A

Outcome Variable	Analysis Set
Study Population/Demography Data	
Disposition of participants	All Enrolled

Outcome Variable	Analysis Set
Demography characteristics	Safety set
Baseline and disease characteristics	Safety set
Important protocol deviations	Safety set
Medical/surgical history	Safety set
Previous anti-cancer therapy	Safety set
Previous radio therapy	Safety set
Concomitant medications/procedures/radiotherapy	Safety set
Efficacy Data	
ORR/BoR	Molecularly eligible centrally confirmed evaluable for response set Evaluable for response set Interim analysis set*
Duration of response	Molecularly eligible centrally confirmed evaluable for response set Evaluable for response set‡ Interim analysis set*
Percentage change in tumour size	Molecularly eligible centrally confirmed evaluable for response set Evaluable for response set◊ Interim analysis set*
PFS	Molecularly eligible centrally confirmed set Safety set Interim analysis set*
CCI	
CCI	CCI
Safety Data	
Exposure	Safety set
AEs	Safety set
Laboratory measurements	Safety set
Vital signs	Safety set
ECG	Safety set
Physical examination	Safety set

Outcome Variable	Analysis Set
Eastern Cooperative Oncology Group performance status (ECOG PS)	Safety set

‡ Only swimmer plot will be provided for this analysis set.
◊ Only spider plot will be provided for this analysis set.
*This analysis set will be used only for interim analysis summary.

Table 6: Summary of outcome variables and analysis sets for Cohort B

Outcome Variable	Analysis Set
Study Population/Demography Data	
Disposition of participants	All Enrolled
Demography characteristics	Safety set
Baseline and disease characteristics	Safety set
Important protocol deviations	Safety set
Medical/surgical history	Safety set
Previous anti-cancer therapy	Safety set
Previous radio therapy	Safety set
Concomitant medications/procedures/radiotherapy	Safety set
Efficacy Data	
Composite response rate	Molecularly eligible centrally confirmed evaluable for response set Evaluable for response set Interim analysis set[Ï]
Duration of composite response	Molecularly eligible centrally confirmed evaluable for response set Evaluable for response set‡ Interim analysis set[Ï]
Percentage Change in tumour size	Molecularly eligible centrally confirmed evaluable for response set Evaluable for response set◊ Interim analysis set[Ï]
Radiological ORR/BoR	Molecularly eligible centrally confirmed evaluable for response set Evaluable for response set Interim analysis set[Ï]

Outcome Variable	Analysis Set
Duration of radiological response	Molecularly eligible centrally confirmed evaluable for response set Evaluable for response set‡ Interim analysis setÏ
rPFS	Molecularly eligible centrally confirmed set Safety set Interim analysis setÏ
PSA	Molecularly eligible centrally confirmed set Safety set* Interim analysis setÏ
CTC conversion	Molecularly eligible centrally confirmed evaluable for response set Evaluable for response set* Interim analysis setÏ
CCI	
CCI	CCI
Safety Data	
Exposure	Safety set
AEs	Safety set
Laboratory measurements	Safety set
Vital signs	Safety set
Physical examination	Safety set
Eastern Cooperative Oncology Group performance status (ECOG PS)	Safety set

* CCI

‡ Only swimmer plot will be provided for this analysis set.

◊ Only spider plot will be provided for this analysis set.

ÏThis analysis set will be used only for interim analysis summary.

4.6 Study Participants

4.6.1 Disposition of Participants

Disposition of all participants who enter the study will be summarised for all enrolled participants. The number and percentages of participants will be presented for the following categories:

- Enrolled (including the screen failures)

- Participants assigned to treatment
- Participants not assigned to study treatment (and reason)
- Received study treatment
- Did not receive study treatment (and reason)
- Participants ongoing with study treatment at data cut off (DCO)
- Participants ongoing in the study at DCO.
- Discontinued from study treatment (and reason)
- Prematurely withdrawn from study (and reason)

Additional listings and summaries on participants affected by the COVID-19 pandemic will also be presented as per standards.

4.6.2 Protocol Deviations

Important protocol deviations (IPDs) are defined as those deviations from the protocol likely to have heavy impact on the interpretation of any analysis based on addressing the primary and secondary objectives of the trial or those may significantly affect a subject's rights, safety or wellbeing.

The following general protocol deviation categories will be programmatically derived from the electronic case report form (eCRF) data. These deviations will be reviewed and assessed on a case-by-case basis by AZ to determine importance. Deviations considered to be important will be listed and discussed in the CSR as appropriate. All decisions on importance will be made ahead of database lock for the primary analysis and will be documented prior to the primary analysis being conducted. Additional non-programmable protocol deviations identified during site visits will be listed as an appendix in the CSR. All IPDs as per the latest PD specifications, not limited to the following will be summarised and listed separately for each module, by cohort and by starting dose of ceralasertib.

- Participants who deviate from inclusion /exclusion criteria per the Clinical Study Protocol (CSP).
- Participants who fail to sign the correct informed consent form for both screening part 1 and part 2, except the genetic informed consent form.
- Participants whose baseline efficacy assessments as per CSP are missing.
- Participants whose baseline safety assessments as per CSP are missing.
- Participants who used disallowed concomitant medications.
- Participants who received prohibited medications during the study. Refer to the CSP Section 6.5 for those medications that are detailed as being 'excluded' from permitted use during the study. This will be used as a guiding principle for the physician review of all medications prior to database lock.
- Participants who received not per protocol (incomplete/overdose) study treatment.
- Study treatment was not given according to protocol.
- Participant has not a histologically confirmed diagnosis of AST (excluding NSCLC) or mCRPC tumour.

- Tumour does not contain a deleterious ATM mutation, tested on a tumour specimen or circulating tumour DNA tested in a locally accredited laboratory using a validated test in line with local regulations.
- Participants with more than 28 days of study drug interruption.
- Persistently missing important protocol required post-baseline safety assessments (vital signs, clinical chemistry/haematology parameters, Hy's Law assessments etc.) and potentially having major impact to participant's safety.
- Baseline RECIST 1.1 scans missing or > 28+ days before treatment assignment.
- Baseline bone scans missing or > 28+ days before treatment assignment.
- Met study treatment discontinuation criteria (e.g., The pregnancy test was positive) however participant was not withdrawn from study treatment but continued study treatment and potentially had major impact to participants' safety according to clinical judgement.
- Persistently missing important post-baseline protocol required efficacy assessments (soft tissue disease progression as defined by RECIST 1.1, bone lesion progression by PCWG-3, radiological progression, CTC count, PSA).

The following will be checked for analysis purposes and will not be included as part of the deviations to be recorded in the protocol deviations log during the study:

- Participants allocated to a treatment but who did not receive any study treatment

During the study, decisions on how to handle errors in treatment dispensing (with regards to continuation/dose reductions/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.

IPDs related to COVID-19 will be summarised as well.

A per-protocol analysis excluding participants with specific important protocol deviations is not planned, however a sensitivity analysis may be performed on the key efficacy endpoints if > 10% of participants in any treatment cohort have any other significant deviation deemed to affect the primary endpoint which haven't already led to exclusion from efficacy analysis.

The need for such a sensitivity analysis will be determined following review of the protocol deviations ahead of database lock and will be documented prior to the analysis being conducted.

4.6.3 Demographic and Other Baseline Characteristics

Module 1

Demographic and other baseline disease characteristics will be summarised and listed for safety set by cohort and by starting dose of ceralasertib.

- Demographics (age [years], age group [18-64 years; 65-84 years; ≥ 85 years], sex [Cohort A], sex [Cohort B: males only], race and ethnicity).
- Participant characteristics at baseline (height [cm], weight [kg], and body mass index [BMI in kg/m^2].

- Previous disease-related treatment modalities.
- Number of regimens of previous chemotherapy
- Disease characteristics at baseline (Eastern Cooperative Oncology Group Performance Status [ECOG PS], primary tumour location, histology type, tumour grade, overall disease classification (local, metastatic, etc), Gleason score [only for Cohort B], CTC count [Cohort B]), CTC status [Cohort B: favourable, unfavourable] ATM mutation [type of mutation, Zygosity], ATM IHC [%]), TNM stages, number of metastatic sites, prior lines of anti-cancer therapies).
- Extent of disease upon entry ([metastatic or locally advanced disease], site of local/metastatic disease, days from recent progression to first day of study treatment)

4.7 Medical and Surgical History

Disease related medical history and relevant surgical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) by system organ class (SOC) and preferred term (PT). All disease related medical history and surgical history (past and current) will be listed, the number and percentage of participants with any medical history will be summarised for safety set by cohort and by starting dose of ceralasertib. Additionally, surgical history will be summarised only for Cohort B safety set.

4.8 Concomitant and Other Treatments

Information on any treatment that the participant is receiving at the time of enrolment and all concomitant treatments given up to 30 (±7) days after discontinuation of study treatment, with reasons for the treatment, dates of administration and the dosage will be recorded in the eCRF. See Section 11.6.5 and Appendix D of CSP for a list of allowed and prohibited medications and anti-cancer treatments for Module 1.

Treatments (including surgery, received prior to, concomitantly, or post-treatment will be coded using the Word Health Organisation (WHO) Drug Dictionary (WHODD) Anatomical Therapeutic Chemical (ATC) classification codes. Concomitant medications will be summarised by ATC classification codes.

For the purpose of inclusion in prior and/or concomitant medication or treatment summaries, incomplete medication or treatment start and stop dates will be imputed as detailed in Section 4.3.3.1 and Section 4.3.3.2.

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

Summaries of all allowed and disallowed concomitant medications with a start date on or before first dose of study treatment and up to the date of last dose of study treatment (inclusive) will be produced.

The number and percentage of participants who took any previous disease-related treatments will be summarised by therapy class (i.e., immunotherapy, hormonal therapy, cytotoxic chemotherapy, systemic therapy, radiotherapy etc.).

The number and percentages of participants with and without prior line of therapies will be provided. Summary statistics will also be provided for the number of regimens of previous chemotherapy.

Missing coded terms will be listed and summarised as "Not coded".

4.9 Efficacy Evaluation

The disease progressions are based on the following criteria depending on specific module evaluation specifications.

4.9.1 Response using RECIST 1.1.

For modules requiring RECIST results, the RECIST tumour response data will be used to determine each participant's visit response according to RECIST version 1.1. It will also be used to determine if and when a participant has progressed in accordance with RECIST 1.1.

Baseline radiological tumour assessments are to be performed no more than 28 days before the first dose/administration of study medication 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 up to 1 year, then every 12 weeks (± 1 week) until objective disease progression.

If an unscheduled assessment is performed, and the participant 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 participants being assessed at a different frequency than other participants.

From the investigator's review of the imaging scans, the RECIST 1.1 tumour response data will be used to determine each participant's visit response according to RECIST version 1.1. At each visit, participants will be programmatically assigned a RECIST 1.1 visit response of CR, PR, SD or PD (see Table 7), 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 participant has had a tumour assessment which cannot be evaluated, then the participant 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.

Table 7 : TL visit responses

Visit Responses	Description
Complete Response (CR)	Disappearance of all TLs. Any pathological lymph nodes selected as TLs must have a reduction in short axis to < 10 mm.
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 ≥ 5 mm, 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

Target Lesions (TLs) – site investigator data

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 participant can have a maximum of 5 measurable lesions recorded at baseline with a maximum of 2 lesions per organ (representative of all lesions involved and suitable for accurate repeated measurement) and these are referred to as target lesions (TLs). If more than one baseline scan is recorded, then measurements from the one that is closest and prior to first dose/administration of study medication will be used to define the baseline sum of TLs. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

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

Note: For participants 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 participant does not have measurable disease at baseline, then the TL visit response will be not applicable (NA).

Rounding of TL data

For calculation of PD and PR for TLs percentage changes from baseline and previous minimum should be rounded to 1 decimal point 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

For a visit to be evaluable all TL measurements should be recorded. However, a visit response of PD should still be assigned if any of the following occurred:

- A new lesion is recorded
- An NTL visit response of PD is recorded
- The sum of TLs is sufficiently increased to result in a 20% increase, and an absolute increase of ≥ 5 mm, from nadir even assuming the non-recorded TLs have disappeared.

Note: the nadir can only be taken from assessments where all the TLs had a LD recorded.

If there is at least one TL measurement missing and a visit response of PD cannot be assigned, the visit response is NE.

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

Lymph nodes

For lymph nodes, if the size reduces to < 10 mm 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 < 10 mm and all other TLs are 0mm then although the sum may be >0 mm 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 < 10 mm 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 still cannot be determined 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. 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 eCRF 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 (at a subsequent visit) 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 participant 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. Participants with intervention are evaluable for CR as long as all non-intervened lesions are 0 (or <10 mm for lymph nodes) and the lesions that have been subject to intervention have a value of 0 (or <10 mm for lymph nodes) recorded. If scaling up is not appropriate due to too few non-missing measurements, then the visit response will be set as NE.

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

Scaling

- If > 1/3 of TL measurements are missing (because of intervention) 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 ≥ 5 mm from nadir).
- If ≤ 1/3 of the TL measurements are missing (because of intervention) 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 29.3 cm. 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 28.4 cm:

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

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.

Lesions that split in two

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

Lesions that merge

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

Change in method of assessment of TLs

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

If a change in method involves clinical examination (e.g., CT changes to clinical examination or vice versa), any affected lesions should be treated as missing.

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 8.

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.
Visit Responses	**Description**
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 participants 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.

CR = complete response; NA = not applicable; NE = not evaluable; NTL = non-target lesion; PD = progressive disease.

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 overtly 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.

Participants 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.

4.9.2 Overall visit RECIST 1.1 response

The previously defined TL and NTL visit responses will be combined with new lesion information to give an overall visit response (see Table 9).

Table 9: 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

TARGET	NON-TARGET	NEW LESIONS	OVERALL VISIT RESPONSE
NA	NE	No (or NE)	NE

Blinded Independent Central Review of Tumour Response

Blinded independent central review (BICR) assessment may be introduced if the cohort is expanded, subject to an approved protocol amendment.

4.9.3 Best Objective Response by RECIST 1.1

Best objective response (BoR) is calculated based on the overall visit responses from each RECIST assessment. It is the best response a participant has had following first dose, 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 using the following response categories: CR, PR, SD, PD and NE.

The confirmation of CR or PR should be performed at the next scheduled 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 intervention. 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.

For participants 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, then BoR will be assigned to the progression (PD) category. For participants who die with no evaluable RECIST assessments, if the death occurs >17 weeks after start of treatment then BoR will be assigned to the NE category.

However, if the participant progresses or dies after two or more missed visits, the participant will be censored at the time of the latest evaluable RECIST 1.1 assessment prior to the two missed visits. NE is not considered a missed visit.

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

4.9.4 Bone progression using PCWG3 visit responses

For modules requiring PCWG3 results, the PCWG3 criteria will be used to determine each participant's visit response. It will also be used to determine if and when a participant has progressed.

Evaluation of Bone progression status

Bone lesions will be assessed by bone scan and will not be part of the RECIST v1.1 malignant soft tissue assessment. Bone lesions identified on a whole-body isotopic bone scan at baseline should be recorded and followed by the same method as per baseline assessment.

In this study isotopic bone scans will be used as a method of assessment to identify the presence of new bone lesions at post-baseline follow-up visits regardless of scheduled or unscheduled. New lesions will be recorded where a positive and unequivocal hot-spot that was not present on the baseline scan assessment is identified on a bone scan performed at any time during the study. The investigator should consider the positive hot-spot to be a significant new site of malignant disease and represent true disease progression in order to record the new lesion.

Baseline radiological tumour assessments are to be performed no more than 28 days before the first dose/administration of study medication and ideally as close as possible to the start of study treatment. Tumour assessments are then performed every 8 weeks (±1 week) following Cycle 1 Day 1 of the study treatment up to 1 year, then every 12 weeks ((±1 week) until radiographic disease progression as defined by RECIST 1.1. (soft tissue; refer to section 4.9.1) and PCWG3 (bone).

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

All bone lesions (or sites of disease) should be identified at baseline. Their status should be followed at subsequent visits. At each visit an overall assessment of the bone lesion progression should be recorded by the investigator.

Progression on a bone scan is identified using PCWG3 as follows:

- At 8 weeks scan:
  2 or more new metastatic bone lesions are observed on the first 8-week scan compared to the baseline assessment. The confirmatory scan, performed at least 6 weeks later and preferably no later than the next scheduled visit for a bone scan (i.e., Week 16), must show 2 or more additional new metastatic bone lesions (for a total of 4 or more new metastatic bone lesions since the baseline assessment) for progression to be documented.
  Note – the first bone scan completed after baseline will be considered the '8-week scan' regardless if taken at week 8 or at an unscheduled assessment.
- After the 8 week scan:
  2 or more new metastatic bone lesions are observed compared to the 8 week assessment. The confirmatory scan, performed at least 6 weeks later and preferably at the next scheduled visit for a bone scan, must show the persistence of or an increase in the number of metastatic bone lesions compared to the prior scan for progression to be documented.

The date of progression is the date of the scan that first documents the second new lesion.

Table 10 provides the definitions for bone progression at each visit for bone lesions.

Table 10: Bone Progression Status

Visit Responses	Description
Non-Progressive Disease (Non-PD)	No evidence of progression, or appearance of one new bone lesion, or non-fulfilment of the progression criteria including new lesions without confirmation of progressions.
Progressive Disease (PD)	Bone lesions fulfilling requirements for at least 2 new lesions and confirmation of progression.
Not Evaluable (NE)	Only relevant if a follow-up scan is not performed.

4.9.5 Best Overall radiological objective response

Overall radiological objective response

The visits responses for soft tissue (according to RECIST 1.1 criteria) and bone progression status (according PCWG3 criteria), and how they are combined to give an overall radiological objective visit response is given in Table 11.

Table 11: Overall Radiological Visit Response

Overall visit soft tissue response (RECIST 1.1)	Bone progression status (PCWG3)	Bone lesions at visit Present/Absent	Overall radiological visit response
CR	Non-PD	Absent	CR
CR	Non-PD	Present	PR
CR	NE	-	PR
PR	Non-PD or NE	Any	PR
SD	Non-PD or NE	Any	SD
NED	Non-PD or NE	Any	Non-PD
NE	Non-PD or NE	Any	PD
PD	Any	Any	PD
Any	PD	Any	PD

CR = complete response; NE = not evaluable (only relevant if a follow-up bone scan is not performed); NED = no evidence of disease (only relevant where there is no TL and NTL from baseline); PD = progressive disease; PR = partial response; SD = stable disease.

Confirmation of response (CR or PR) should be performed at the next scheduled RECIST and PCWG3 assessment (and must not be less than 4 weeks later) following the date the criteria for response were first met (see Table 12).

Table 12: Best Overall Radiological Response When Confirmation of CR and PR Required

Overall radiological response first time point	Overall radiological response subsequent time point	Best overall response
CR	CR	CR
CR	PR	SD, PD or PRa
CR	SD	SD or PD
CR	PD	SD or PD
CR	NE	SD or NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD or PD
PR	NE	SD or NE
NE	NE	NE

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.
[a] If a CR is truly met at first time point, then any disease seen at subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scan suggest small lesions were likely still present and in fact the participant had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

4.9.6 Radiological progression.

The analysis of radiological progression will be based on tumor assessments using RECIST 1.1 (soft tissue) and PCWG3 (bone) criteria.

Participants who have not progressed (i.e., who have a CR, PR, or SD by RECIST 1.1, and non-progressive for bone disease by PCWG3) at the time of analysis will be censored at the time of the latest date of their last evaluable RECIST assessment or bone scan assessment that showed fewer than 2 new lesions.

However, if the two or more consecutive scheduled radiological assessments immediately prior to progression or death were missing, the participant will be censored at the time of the latest evaluable RECIST 1.1 and bone scan assessment prior to the two or more missed assessments. (Note: NE visit is not considered as missed visit).

If the participant has no evaluable visits or does not have baseline data, he will be censored at Day 1 unless he dies within two visits of baseline (in which case the participant's date of death will be used). The rPFS time will always be derived based on scan/assessment dates, not visit dates.

When the investigator is in doubt as to whether PD has occurred and therefore reassesses the participant at a later date, the date of the initial scan should be declared as the date of progression if the repeat scans confirm progression.

The requirements for determination and confirmation of radiographic progression by either bone scan (bone progression) or CT/MRI (soft tissue progression) are summarised in Table 13.

Table 13 : Requirements for Documentation of Progression

Visit Date	Criteria for Bone Progression	Criteria for Soft Tissue Progression
First visit after Baseline (expected week 8)	Two or more new lesions compared to baseline bone scan. Requires confirmation at least six weeks later with >2 additional lesions compared to the first scan after baseline	Progressive disease on CT or MRI by RECIST 1.1 No confirmation required.
From the 2nd visit after Baseline	Two or more new lesions compared to the first bone scan after baseline. Requires confirmation at least six weeks later for persistence or increase in number of lesions.	Progressive disease on CT or MRI by RECIST 1.1. No confirmation required.

4.9.7 CTC count conversion

Conversion of CTC count is defined as a change from unfavourable at baseline (CTC ≥ 5/7.5 mL blood) to favourable at post-baseline (CTC < 5/7.5 mL blood) (as per PCWG3 criteria) prior to radiological progression. Post-baseline result will be confirmed with a second consecutive value obtained three or more weeks later.

4.9.8 PSA progression using PCWG3 criteria.

The PSA progression is defined as a 25% or greater increase and absolute increase of ≥ 2ng/ml above the nadir beyond 12 weeks. This must be confirmed by a second consecutive measurement value obtained at least 3 weeks later but within 12 weeks.

4.9.9 Composite response

Composite response will be defined on the basis of the following outcomes; if any of these occur in the absence of radiological or PSA progression (according to RECIST 1.1 for soft tissue and visceral

lesions, PCWG3 criteria for bone lesions, and PSA) participants will be considered to have responded:

- Investigator assessed radiological objective response by RECIST 1.1 for soft tissue and visceral lesions and PCWG3 criteria for bone lesions. Response must be confirmed at least 4 weeks later. Blinded Independent Central Review (BICR) assessment may be introduced if the cohort is expanded, subject to a protocol amendment.
- Conversion of CTC count from ≥ 5/7.5mL blood (unfavourable) at baseline to < 5/7.5mL blood (favourable) (as per PCWG3 criteria) confirmed by a second consecutive value obtained 3 or more weeks later.
- PSA decline of ≥ 50% confirmed by a second consecutive measurement at least 3 weeks later (based on PCWG1 criteria).

For visits with non-evaluable radiological response, absence of radiological progression for that specific visit can be decided if there is any subsequent evaluable non progression response (CR/PR/SD). For visits with missing PSA assessment, absence of PSA progression for that specific visit can be decided if there is any subsequent non progressive PSA assessment available. Participants who discontinue study treatment without progression, receive a subsequent anti-cancer therapy and then respond will not be included as responders. More details on the derivation of composite response may be provided in in a separate programming guidance document if deemed necessary.

4.10 Analysis and Data Conventions

Each cohort will be analysed separately for the primary, secondary and exploratory endpoints. No formal statistical hypotheses will be conducted for this module. See Section 4.22 for the justification of the sample size.

4.11 Multi-centre Studies

No adjustments for centre will be performed for this module.

4.12 Adjustments for Covariates

No adjustments for covariates will be done for this module.

4.13 Multiple Comparisons/Multiplicity

Not applicable.

4.14 Interim Analysis.

An administrative interim analysis will be conducted for Cohort A approximately 4 months after approximately 18 molecular eligible centrally confirmed evaluable for response participants have been enrolled. The assessment of key efficacy and safety will be performed. The purpose for this administrative interim is to inform internal decision making only with no planned adaptions to the study.

A futility interim analysis will be conducted for Cohort B approximately 6 months after at least 12 molecularly eligible centrally confirmed evaluable for response participants have been enrolled . The futility stopping rule for the prostate cohort will be based on the primary endpoint, composite response. CCI
CCI
CCI This stopping rule is for guidance only, and any decision to cease recruitment will be based on sponsor review of all safety and efficacy clinical data available. For the interim analysis, data will be analysed and summarised in an unblinded fashion as outlined in this document.

The participant disposition, key baseline characteristic and key safety outcomes will be summarised. The primary and key secondary endpoints will be summarised as specified in Section 4.16 and Section 4.17 respectively. The list of tables, listings and figures required for interim analysis will be prepared as per AZ standards; and they will be flagged separately in the list of tables, listings and figures (which will be a separate document) for the entire study.

An additional 'interim analysis set' is defined as all subjects in the 'Molecular eligible centrally confirmed evaluable for response' set with chance to have at least two follow up RECIST assessments. This interim analysis set will be used for the evaluation of the primary and key secondary efficacy endpoints (ORR, BoR, etc).

4.15 Examination of Subgroups

The following subgroups will be analysed for the primary and secondary tumour response endpoints in this module:

- CCI
- CCI
- CCI
- CCI
- CCI
- CCI
- CCI

4.16 Primary Efficacy Variables

The primary and secondary efficacy summaries and figures will be provided only for the participants who received 160 mg BID ceralasertib as starting dose on Cycle 1 Day 1. Listings will be provided for all participants irrespective of their starting dose of ceralasertib.

4.16.1 Objective Response Rate (Cohort A)

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

A participant 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.

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. Participants who discontinue study treatment without progression, receive 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 participant to be considered as a responder).

In the case where a participant 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 participant will be defined as a responder. Similarly, if a participant 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.

The ORR will be based on the investigator RECIST data and using all scans regardless of whether they were scheduled or not.

Summaries will be produced that present the number and percentage of participants with a tumour response (CR/PR) based on molecularly eligible centrally confirmed evaluable for response set as well as evaluable for response set. A two-sided 80% confidence interval using Clopper-Pearson method will also be computed.

4.16.2 Composite Response Rate (Cohort B)

Composite Response Rate (CRR) is defined as the percentage of participants who have a composite response as defined in section 4.9.9. The composite response rate will be calculated for molecularly eligible centrally confirmed evaluable for response set as well as evaluable for response set.

Data obtained up until progression, or last evaluable assessment in the absence of progression, will be included in the assessment of CRR. Participants who discontinue study treatment without progression, receive a subsequent anti-cancer therapy and then response will not be included as responders in the CRR (i.e. both visits contributing to a response must be prior to subsequent therapy for the participant to be considered as a responder).

The CRR will be based on the investigator RECIST data and all scans regardless of whether they were scheduled or not.

Summaries will be produced that present the number and percentage of participants with a composite response. A two--sided 80% confidence interval using Clopper-Pearson method will be computed for response rate.

A by module, by cohort, by subject (subject identifier, centrally confirmed NGS result and IHC level) listing of composite response components (best overall radiological response, CTC conversion status, PSA decline, overall composite response, etc) will be provided.

4.17 Secondary Efficacy Variables

4.17.1 Duration of Response (Cohort A)

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 participant does not progress following a response, then their duration of response will use the PFS censoring time (see Section 4.17.3).

Descriptive data will be provided for the duration of response in responding participants, including the associated Kaplan-Meier estimate of median duration of response, where there are sufficient number of responders based on molecularly eligible centrally confirmed evaluable for response set as well as evaluable for response set. A Kaplan-Meier plot and a swimmer plot will also be provided.

4.17.2 Percentage change in tumour size (Cohort A and Cohort B)

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 for which data are available will be obtained for each participant taking the difference between the sum of the target lesions at each week 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).

The absolute change and percentage change from baseline in the sum of tumour size at each assessment will be calculated. The best percentage change in tumour size from baseline will be 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. The best percentage change in tumour size will include all assessments prior to the earliest of death in the absence of progression, any evidence of progression, the start of subsequent anti-cancer therapy, or the latest evaluable RECIST assessment if the participant has not died, progressed or started subsequent therapy. Change in tumour size at progression or the latest evaluable RECIST assessment (as applicable) should be included in the determination of best percentage change in tumour size.

If best percentage change cannot be calculated due to missing data (including if the participant has no TLs at baseline), a value of +20% will be imputed as best percentage change from baseline in the following situations (otherwise best percentage change will be left as missing):

- If a participant has no post-baseline assessment and has died
- If a participant has new lesions or progression of NTLs or TLs
- If a participant has withdrawn due to PD and has no evaluable TL data before or at PD

The best percentage change in TL tumour size from baseline will be summarised descriptively for molecularly eligible centrally confirmed evaluable for response set as well as evaluable for response set. The number and percentage of participants whose best percentage change data is imputed will also be presented.

Best percentage change will be presented graphically using a waterfall plot to present each participant's best percentage change 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 corresponds with the definition of a 'partial response' and another refence line at the +20% change in TL tumour size 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 progression on the best percentage change in TL tumour size at a particular timepoint will be based upon the 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 are ordered in descending order with imputations due to death appearing first followed by a gap followed by all other participants. Imputed values will be clearly marked with '*' and participants with imputation where there was a death or evidence of progression will have different shading to each other and the other participants to make it clear that these are different.

Additionally, best percentage change in tumour size will be presented graphically using waterfall plots, where best percentage change in TL tumour size as a separate bar ordered from the largest increase to the largest decrease, colour coded in respective figures by mutation categories/gene variant categories and best objective response categories marked with appropriate symbols on top of each bar.

Additional, 'spider' plots will be produced. This depicts each participant's percentage change in TL tumour size as a line over time and progression due to NTL or new lesions will be indicated (imputed data will not be included in the plots).

4.17.3 Progression free Survival (Cohort A)

PFS is defined as the time from first dose until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the participant 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). Participants 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 latest evaluable RECIST

assessment. However, if the participant progresses or dies after two or more missed visits, the participant will be censored at the time of the latest evaluable RECIST 1.1 assessment prior to the two missed visits. NE is not considered a missed visit.

Given the schedule of RECIST assessments (i.e., every 8 weeks for the first year and every 12 weeks there after until a confirmed progression) two missing visits will equate to 18 weeks in the first year (i.e., 2x8=16 weeks + 1 week for early assessment +1 week for a late assessment=18 weeks), 26 weeks in the subsequent years (i.e., 2x12=24 weeks + 1 week for early assessment +1 week for a late assessment=26 weeks) after the first treatment allowing for early and late visits.

If the participant has no evaluable visits or does not have baseline data, they will be censored at Day 1 unless they die within 17 weeks (16 weeks plus 1 week allowing for a late assessment within the visit window).

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

RECIST 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 participant for PFS the participant 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.

Analyses of PFS will be based upon the molecularly eligible centrally confirmed set and safety analysis set.

A time to progression swimmer plot and aKaplan-Meier plot of PFS will be presented. Median PFS with respective 80% CIs will be estimated using the Kaplan-Meier technique. Summaries of the number and percentage of participants experiencing a PFS event, and the type of event (progression or death) will be provided along with the proportion of participants alive and progression free at three months, six months, nine months and twelve months calculated using the Kaplan-Meier (KM) technique. Median and range of follow up duration for censored participants will be provided as well.

4.17.4 Radiological Objective Response Rate (Cohort B)

Radiological ORR is defined as the percentage of participants who have a confirmed investigator assessed response of CR or PR in their soft tissue disease assessed by RECIST 1.1 and bone scan status of non-PD or NE for their bone disease assessed by PCWG-3, and will be based on the molecularly eligible centrally confirmed evaluable for response set as well as evaluable for response set, and on a subset of participants with measurable disease in the molecularly eligible centrally confirmed evaluable for response set.

A confirmed response of CR/PR means that a response of CR/PR is recorded at 1 visit and confirmed by repeat imaging not less than 4 weeks after the visit when the response was first observed with no evidence of progression between the initial and CR/PR confirmation visit.

Data obtained up until progression, or last evaluable assessment in the absence of progression, will be included in the assessment of rORR. Participants who discontinue study treatment without progression, receive a subsequent anti-cancer therapy and then respond will not be included as responders in the rORR (i.e. both visits contributing to a response must be prior to subsequent therapy for the participant to be considered as a responder).

In the case where a participant 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 participant will be defined as a responder. Similarly, if a participant 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.

The rORR will be based on the investigator RECIST data and using all scans regardless of whether they were scheduled or not.

Summaries will be produced that present the number and percentage of participants with a tumour response (CR/PR) based upon the number of participants with measurable disease at baseline per site investigator. A two-sided 80% confidence interval using Clopper-Pearson method will also be computed.

4.17.5 Duration of rORR (Cohort B)

The duration of radiological objective response is defined as the time from the date of first documented radiological response until date of objective radiologic disease progression or death. Descriptive data will be provided for the duration of response in responding participants, including the associated Kaplan-Meier estimate of median duration of response, where there are sufficient number of responders in the efficacy datasets as specified in Table 6. A Kaplan-Meier plot and a swimmer plot will also be provided.

4.17.6 Percentage of CTC count conversion from unfavourable to favourable (Cohort B).

Conversion of CTC count is defined as a change from unfavourable at baseline (CTC $\geq$ 5/7.5 mL blood) to favourable at post-baseline (CTC < 5/7.5 mL blood). Post-baseline result will be confirmed with a second consecutive value obtained three or more weeks later prior to radiological progression. Participants who discontinue study treatment without progression, receive a subsequent anti-cancer therapy and then respond will not be included as responders. The percentage of participants with CTC count conversion will be presented on those with unfavourable CTC at baseline. Summaries will be produced that present the number and percentage of participants with a CTC conversion for molecularly eligible and centrally confirmed evaluable for response set and evaluable for response set. A two-sided 80% confidence interval using Clopper-Pearson method will also be computed.

4.17.7 Confirmed PSA decline (Cohort B)

Confirmed PSA decline is defined as a PSA reduction greater than 50% from baseline which is confirmed later by a second consecutive measurement done at least three weeks later prior to radiological progression. Participants who discontinue study treatment without progression, receive a subsequent anti-cancer therapy and then respond will not be included as responders. The proportion of participants with confirmed PSA decline will be presented on the molecularly eligible and centrally confirmed set and safety analysis set. Summaries will be produced with the number and percentage of participants with confirmed PSA decline at DCO and a two-sided 80% confidence interval using Clopper-Pearson method.

4.17.8 rPFS (Cohort B)

Radiological PFS is defined as the time from the start of treatment until the date of objective radiographic disease progression or death. Participants who have not progressed (i.e., who have a CR, PR or SD by RECIST 1.1, and nonprogressive disease by PCWG-3) at the time of analysis will be censored, the latest date of their last evaluable RECIST 1.1 assessment or bone scan assessment that showed fewer than 2 new lesions. However, if the 2 or more consecutive scheduled radiographic assessments immediately prior to progression or death were missing, the participant will be censored at the time of the latest evaluable RECIST 1.1 and bone scan assessment prior to the 2 or more missed assessments. If the participant has no evaluable visits or does not have baseline data, they will be censored at Day 1 unless they die within 2 visits of baseline (in which case the participant's date of death will be used). The rPFS time will always be derived based on scan/assessment dates, not visit dates. When the investigator is in doubt as to whether progressive disease has occurred and therefore reassesses the participant at a later date, the date of the initial scan should be declared as the date of progression if the repeat scans confirm progression. Analyses of rPFS will be based upon the molecularly eligible and centrally confirmed set and safety analysis set. KM plots of rPFS will be presented. Summaries will include the median rPFS with respective 80% CIs calculated using the Kaplan-Meier technique. Summaries will also provide the number and percentage of participants experiencing a rPFS event, and the type of event (radiological progression or death), along with the proportion of the participants alive and progression free at three months, six months, nine months and twelve months using KM technique. A 80% confidence interval for the survival estimates will be provided.

4.18 Exploratory endpoints

4.18.1 CCI [redacted]

CCI [redacted].

4.18.2 CCI [redacted]

CCI [redacted]

[redacted]

4.18.3 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted].

[redacted]

[redacted]

4.18.4 [redacted]

[redacted]

4.19 Safety Evaluation

All safety summaries and analyses will be based upon the Safety Set as defined in Section 4.5.

4.19.1 Extent of exposure and dose intensity

4.19.1.1 Duration of exposure

Exposure data will be summarised and listed for the Safety Analysis Set (see Section 4.5).

Extent of exposure of ceralasertib monotherapy (previously known as AZD6738) 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).

Since the planned schedule is to take ceralasertib continuously for the first 14 days in the cycle, Z=14

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

where total treatment duration will be calculated as above, and a dose interruption not in accordance with the protocol is defined as number of days where the participant has not taken any planned dose, due to toxicity or participant miss/forget to take the treatment dose. The treatment duration calculation makes no adjustment for any dose reductions that may have occurred.

Missed or forgotten doses

Missed and forgotten doses should be recorded on the DOSE module as a dose interruption with the reason recorded as "Subject 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.

Participants who permanently discontinue during a dose interruption

If a participant permanently discontinues study treatment during a dose interruption, then the date of last administration of study medication recorded on DOSDISC will be used in the programming.

4.19.1.2 Relative dose intensity

Relative dose intensity (RDI) will be calculated as appropriate. RDI is the percentage of the actual dose delivered relative to the intended dose through to treatment discontinuation and is helpful to summarise dose reductions. Relative dose intensity will be defined as follows:

RDI(%)= d/D ×100 where

- d is the actual cumulative dose delivered up to the actual last day of dosing.
- D is the intended cumulative dose up to the actual last day of dosing. D is the total dose that would have been delivered if there were no modification to dose or schedule.

Duration of dose delays will be derived for doses indicated as being delayed on the eCRF. For each individual dose, the duration of dose delay is the number of days the dose was received outside of the original planned dosing schedule. Overall duration of dose delays will be calculated as the sum of all individual dose delays during the study. For example, assume the eCRF indicate that there was a treatment delay (question "Treatment delayed" indicated as "Y" by investigator) then the duration of the individual delay will be [date first dose received after delay – date last dose received before delay +1].

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 discontinuation form 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.

In addition, the number and percentage of participants who received the planned starting dose of ceralasertib, with no interruption, with dose interruption, dose reduction and cycle delay will be presented. Reason for dose interruption, dose reduction and cycle delay will also be summarised and listed.

4.19.2 Adverse Events

AEs and SAEs will be collected from the time of signature of informed consent form and throughout the treatment period including those occurring within 30 (±7) days of follow-up period after IP discontinuation.

Summary tables will include adverse events, if they onset or worsen (by investigator report of a change in CTCAE grade), during the treatment period as defined in the CSP or during the 30-day safety follow-up period. That is, pre- and post-treatment AEs will be included in the data listings (flagged) but will not be included in the summary tables of AEs. Any AE occurring past the defined thirty (30) days safety follow-up period after IP discontinuation, or after a participant has received further therapy for cancer will be flagged in the data listings.

During the evaluation of the AE data prior to lock, an AZ medically qualified expert will review the list of AEs that were not reported as SAEs and AEs leading to discontinuation of study treatment. Based on the expert's judgment, significant AEs of particular clinical importance may, after consultation with the Global Participant Safety Physician, be considered other significant AEs (OAEs) and reported as such in the CSR. A similar review of laboratory/vital signs/ECG data will be performed for identification of OAEs.

Examples of these could be marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment.

Some clinical concepts (including some selected individual preferred terms and higher-level terms) are considered to be "AEs of special interest" (AESIs). AESIs represent pre-specified risks that are considered to be of importance to a clinical development program. These AESIs, if applicable, will be identified as a list of categories provided by the participant safety team.

Reviews will take place prior to database lock to determine whether any AE should be classified as AESIs. The review will identify which higher-level terms, and which preferred terms should contribute to each AESI.

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 Common Terminology

Criteria for Adverse Events (CTCAE) grade, relationship to study treatment, action taken and outcome. Frequencies and percentages of participants reporting each preferred term will be presented (i.e., multiple events per participant will not be accounted for, except for event level summaries).

AEs will be summarised by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and MedDRA preferred term (PT) for safety set by module, by cohort as well as by module, by cohort, by ATM gene variant (germline/somatic). For each SOC/PT, the number and percentage of participants reporting at least one occurrence will be presented i.e., for a participant, multiple occurrences of an AE will be only counted once. If a participant reports multiple occurrences of the same AE, the participant will be summarised only for the maximum reported CTCAE grade.

Most common AEs and most common AEs of CTCAE grade 3 or higher will also be summarised separately by MedDRA PT as well as by MedDRA PT, by ATM gene variant, where most common is defined as a frequency > 5% in each dose group by starting dose received by participants.

An overall summary table (the number and percentage of participants with at least 1 AE by Module be tabulated for:

- All AEs.
- Any AE causally related to treatment.
- Any AE of CTCAE grade 3 or higher.
- Any AE of CTCAE grade 3 or higher causally related to treatment.
- Any AE with an outcome of death.
- Any AE with an outcome of death causally related to treatment.
- All SAEs.
- Any SAEs causally related to treatment.
- Any AE leading to discontinuation of study treatment.
- Any AE leading to discontinuation study treatment, casually related to study treatment
- Any AE leading to dose reduction.
- Any AE leading to dose interruption.
- Any AE leading to dosing cycle delays/treatment delays.
- Any SAE leading to discontinuation of the study treatment
- Any SAE leading to discontinuation study treatment, casually related to study treatment
- OAEs
- AESIs (if applicable)

Covid-19 and related AEs will also be collected and reported by MedDRA SOC/PT.

4.19.3 Deaths

Details of any death will be listed.

4.19.4 Clinical Laboratory Evaluation

For by-visit summaries, the last non-missing assessment (including repeat assessments) recorded at each visit will be summarized. If visit windows are to be used, the non-missing assessment closest to

the mid-point of the visit window will be summarized (including repeat and unscheduled assessments). For across visit summaries (e.g., maximum post-baseline value), scheduled, unscheduled and repeat assessments will be considered. Clinical laboratory evaluation summaries will be provided for safety sets, which will only include the parameters specified in Table 14.

All laboratory results collected will be listed.

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.

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 participant, 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 participant 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 and change from baseline will be summarised using descriptive statistics at each scheduled assessment time by actual treatment group.

A summary and a listing of key subject information on treatment emergent (defined from start of treatment to 30 (±7) days following the last dose of study treatment) changes outside predefined criteria will be provided. The following clinical chemistry parameters – sodium, potassium, calcium and glucose, will be summarised as bidirectional shift tables. CTCAE grade changes from baseline to the maximum grade on-treatment will be presented on both unidirectional and bidirectional shift tables. In addition, the number of participants 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.

Table 14 : Laboratory Safety Variables

Haematology (whole blood)	**Clinical chemistry (serum or plasma)**
Blood (B)-Haemoglobin	Serum (S)/Plasma (P)-Albumin
B-Leukocyte count	S/P-Alanine transaminase (ALT)
B-Leukocyte differential count (absolute count)[a]	S/P-Aspartate transaminase (AST)
Neutrophils	S/P-Alkaline phosphatase
Lymphocytes	S/P-Bilirubin, total
Monocytes	S/P-Calcium, total
Basophils	S/P-Creatinine
Eosinophils	S/P-Glucose

B-Platelet count	S/P-Magnesium
B-reticulocytes[b]	S/P-Phosphate
Coagulation	S/P-Potassium
B-INR	S/P-Sodium
APTT	S/P- Urea nitrogen or Urea
Urinalysis (dipstick)	S/P- C - reactive protein
U-Protein	S/P- Thyroid stimulating hormone (TSH)[c]
U-Glucose	
U-Blood	
Other Screening tests	
Serum (screening) and urine (other time points) human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential) Serum testosterone	

[a] If absolute differentials not available please provide % differentials.

[b] If absolute particle counts not available please provide relative particle count.

[c] Free triiodothyronine (T3) or free thyroxine (T4) will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.

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. Box 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 participants 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.

4.19.5 Vital Signs

Absolute values and change from baseline for pulse, systolic and diastolic blood pressure, body temperature and weight will be summarised by Module, by cohort and visit. Box plots of absolute values and change from baseline values for all vital signs will also be presented.

A shift table of baseline to maximum value on treatment for blood pressure and pulse will also be presented using the normal ranges in Table 15.

There will be no imputation for missing values. Observed values and changes from baseline will be compared to the relevant AZ defined reference ranges for vital signs and clinically important change criteria. Any value (observed and change) falling outside the reference range will be flagged.

Table 15: AstraZeneca defined reference ranges for vital signs variables

Vital sign (unit)	Outside AZ defined minimum reference range	Outside AZ defined maximum reference range	Treatment emergent decrease minimum	Treatment emergent increase maximum
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		

SPB systolic blood pressure.
DBP diastolic blood pressure.

4.19.6 Physical examination findings

A complete physical examination will be performed at Screening Part 2 (Visit 2), at all on-treatment visits, at study treatment discontinuation and at safety follow-up.

Body weight and height will be measured for the calculation of Body Mass Index (BMI). All baseline physical examination findings will be summarised by module, by cohort.

All abnormal findings from the physical exam in the post-baseline visits will be reported and analysed under AEs.

4.19.7 ECG Variables

Not applicable.

4.19.8 Eastern Cooperative Oncology Group performance status (ECOG PS)

ECOG performance status scores will be collected for all participants at baseline and at on-treatment visits as described in SoA (see Table 3 Schedule of Assessments in CSP). A shift table of baseline to maximum on treatment for ECOG PS will be summarised by module, by cohort, by performance status grade (0-4) (See section 8.2.3 of the CSP).

4.20 CCI [redacted]

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CCI [redacted]

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4.21 CCI

CCI .

4.22 Sample Size considerations

4.22.1 Module 1

The primary objective of this study is to determine investigator assessed objective response rate (Cohort A) and composite response rate (Cohort B) of study intervention. The number of molecularly eligible centrally confirmed participants has been based on the desire to obtain adequate response, tolerability, safety, CCI while exposing as few participants as possible to study intervention and procedures. If there is a discordance between the local and central lab testing, additional participants may be enrolled to the study to maintain the intended sample size.

In Cohort A, the sample size of ~25 participants is expected to give adequate precision in the estimate of the ORR. CCI

In Cohort B, the sample size of ~27 participants is expected to give adequate precision in the estimate of composite response. CCI

CCI

CCI

CCI

Based on the primary outcome on the molecular eligible and centrally confirmed evaluable for response set, CCI

CCI

For cohort A, with the CCI and CCI

- CCI [redacted]
- CCI [redacted]

For cohort B, with the CCI [redacted] and CCI [redacted]

- CCI [redacted]
- CCI [redacted]

4.23 Changes in the Conduct of the Study or Planned Analysis

Not Applicable to this study

5 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 Recommendations from the Prostate Cancer Clinical Trials Working Group 3. J Clin Oncol 34:1402-1418. © 2016 by American Society of Clinical Oncology.
4. SAS Institute Inc. 2013. SAS® 9.4 Statements: Reference. Cary, NC: SAS Institute Inc.
5. 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.
6. CCI [redacted]

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