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Document title: A Phase II, Open-label Study to Assess the Efficacy, Safety, and Tolerability of AZD4635 in Combination with Durvalumab and in Combination with Cabazitaxel and Durvalumab in Patients Who Have Progressive Metastatic Castrate-Resistant Prostate Cancer (AARDVARC)
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Parexel International

AstraZeneca

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A Phase II, Open-label Study to Assess the Efficacy, Safety, and Tolerability of AZD4635 in Combination with Durvalumab and in Combination with Cabazitaxel and Durvalumab in Patients Who Have Progressive Metastatic Castrate-Resistant Prostate Cancer (AARDVARC)

Statistical Analysis Plan

Version: 4.0

Parexel Project Number: CCI

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REVISION HISTORY

Version No.	Effective Date	Summary of Change(s)
1.0	23 July 2020	New document
2.0	24 Feb 2021	Due to Protocol updated, the changes as following: 1. Schedule of Activities updated as per Protocol Amendment version 2. 2. Enrolment in Arm A was stopped before reaching initially planned number of 80 participants. Ongoing participants in Arm A may continue treatment as planned (ie, as long as they receive clinical benefit and do not meet any discontinuation criteria). 3. The secondary objective related to the analysis of efficacy endpoints by adenosine (ADO) signalling gene expression in high and low subgroups was limited to Arm B and rPFS. CCI [redacted] 4. Exclusion criteria 9 of core CSP was added to section 2.2 as important protocol deviation (IPD). 5. The safety review committee (SRC) decision will be shared with all investigators, but statement that this should occur prior to further dosing of participants on Arm B was deleted. 6. The data cut-off (DCO) for primary analysis and reporting defined for Arm B will be used for both treatment arms. 7. For Arm B, the DCO was changed to when approximately 60% of events (death or progression) occur. 8. The number of Arm B participants requiring intensive PK sampling was increased from 6 to 12 evaluable participants. 9. Summary tables will not be produced for Arm A, Data from Arm A will be listed only.

		10. The futility interim analysis for Arm A was removed. A futility interim analysis was added for Arm B. 11. Section 6 Interim analysis was updated following AstraZeneca team's suggestion. The updates as below was for clarity and consistency: 1 PID was removed from abbreviation list; QD, Q3W and Q4W was added to abbreviation list. 2 The definition of IPD was added to section 2.2 Protocol Deviations. 3 The following text was added to section 2.2 Protocol Deviations "Important protocol deviations and any action to be taken regarding the exclusion of participants or affected data from specific analyses are defined in the project-specific Protocol Deviation Specification.". 4 The following text was added under section 3.3.3 Objective response rate (ORR) "For the secondary endpoint ORR assessed by RECIST 1.1 and PCWG3, only dosed participants with measurable disease (target lesions) at baseline will be included in the analysis. A participant will be classified as a responder if the RECIST 1.1 criteria for a CR or PR are satisfied (as well as the absence of confirmed progression on bone scan assessed by PCWG3)." 5 5The following text was added to section 3.3.6 Change in tumour size. "Whenever TL tumour size data for the week XX visit (Note: or visit at which progression was documented if before week XX) is available then this should be used in the analysis. A windowing rule will be applied and will follow the protocol allowed visit window; therefore any RECIST scan performed within ± 7 days of the protocol scheduled visit will be used for that visit." 6 The following text was added to section 3.4.1 Functional assessment of cancer therapy – prostate cancer (FACT-P). "The FACT

		Advanced Prostate Symptom Index-8 [FAPSI-8], a symptom score made up of 8 items from within the FACT-P (pain [n=3], fatigue [n=1], weight loss [n=1], urinary conditions [n=2], and concerns about the condition getting worse [n=1]).” 7 The molecular weight and free fraction values was added to section 3.7.2 Pharmacokinetic parameters. 8 Section 4.2.1.6 Prior therapies was updated as per latest TFL shells for consistency. The updates as below was for correction: 1. “Prior therapy can be in either the hormone-sensitive or the hormone-refractory setting” in inclusion criteria 10 of core CSP was added in section 2.2 Protocol Deviations. 2. TL visit responses subsequent to CR in section 3.2.1 Target lesions was updated following AstraZeneca team’s suggestion. 3. The calculation of percentage intended dose (PID) was removed from section 3.6.2 Dose intensity following AstraZeneca team’s suggestion. 4. Duplicate text from section 3.7.2 Pharmacokinetic parameters was removed. 5. λz span was added to PK diagnostic parameters list in section 3.7.2 Pharmacokinetic parameters. 6. Disallowed concomitant medication in section 4.2.1.7 Concomitant medications was updated following AstraZeneca team’s suggestion. 7. The following text in section 4.2.3.2 “Stacked bar chart will be used to display proportion of participants in improved, stable, or deteriorated” was removed. 8. The following text was added in section 4.2.4.2 Adverse Events/Serious adverse events. “Number and percentage of participants with adverse events, most common (frequency of >10%) will be summarised by preferred term in Arm B.” 9. The following analysis in section 4.2.4.2 Adverse Events/Serious adverse events was considered as unnecessary analysis and was removed as per AZ study team “At least one

		AESI possibly related to study medication", "At least one AESI leading to discontinuation of study medication" and "A summary of total duration (days) of AESI will be provided for events which have an end date and this may be supported by summaries of ongoing AESIs at death and, separately, at data cut-off." 10. The summary of QTcF in section 4.2.4.3Electrocardiographic (ECG) was updated as below: QTcF and QTcF intervals were summaries at any observation instead of maximum on treatment following AZ Corporate CSRHLD table templates v3.4. 11. The summary and listing of WHO performance status was removed. 12. The descriptive statistics in section 4.2.5.1 Plasma concentration data and section 4.2.5.2 Pharmacokinetic Parameters was updated, the following text was added following the requitement of AZ Corporate CSRHLD table templates v.3.4. • The geometric standard deviation (geoSD, calculated as exp[s], where s is the standard deviation of the data on a loge scale) • Gmean + geoSD (calculated as exp[μ+s]) • Gmean – geoSD (calculated as exp[μ-s]) The update as below following the latest CRF update: 1. "The number and percentage of participants with at least one dose interruption and dose reductions for AZD4635, the number and percentage of participants with at least one delay and at least one dose interruption and for Durvalumab, the number and percentage of participants with at least one delay, at least one dose reduction and at least one dose interruption for Cabazitaxel will be presented" was edited in section 4.2.4.1 Exposure. The update as below following the latest request from AZ study team: 1. Interim tumour response evaluable and interim PSA evaluable analysis sets were added to section 2.1. 2. New text added for the analysis of best objective response and PSA response for interim analysis: "Best objective response will

		be produced for interim tumour response evaluable analysis set and PSA response will be produced for interim PSA evaluable analysis set. 80% CI instead of 95% CI of best objective response rate and PSA_{50} response rate will be presented for the interim analysis". 3. New text added in section 4.2.4.2: "Number and percentage of participants with adverse events possibly related to any study treatment will be summarised by system organ class, preferred term and maximum reported CTCAE grade for Arm B." and "Number and percentage of participants with adverse events possibly related to any study treatment, most common (frequency of >10%) will be summarised by preferred term for Arm B".
3.0	14 May 2021	1. The update as below following the latest request from AZ study team: 2. Interim tumour response evaluable in section 2.1 Table 2 was changed from 17 weeks to 19 weeks as Arm B has RECIST every 9 weeks. 3. Interim PSA evaluable in section 2.1 Table 2 was changed from 13 weeks to 85 days, which is start of week 13. 4. Surgical history and PK outputs were removed from section 6. 5. Treatment emergent AE were updated as: Treatment emergent AE is defined as adverse events with an onset date on or worsen after the date of first dose and up to and including 30 days following the date of last dose of AZD4635 or Cabazitaxel, whichever occur later, or adverse events with an onset date on or worsen after the date of first dose and up to and including 90 days following the date of last dose of Durvalumab. 6. AESI flag was added to the AE listing section 4.2.4.2. 7. The following text was removed from section 4.2.2.4 8. "Specifically, these plots will be based on the sum of diameters as entered in the database including no adjustment as a function of tumour response in the case of participants with lymph node regression.".

		9. "If required," was added at the beginning of section 4.2.6.
4.0	20Apr2022	1. Immune Mediated Adverse Events (imAE) in section 3.6.3 were updated as "Immune Mediated Adverse Events (imAE) is defined as a subset of AESI which consider interventions of corticosteroids, immunosuppressants, and/or endocrine therapy; are deemed consistent with having an immune-mediated mechanism of action and where there was no clear alternative etiology. Automated adjudication approach via programming will be applied to identify imAEs, and will be reported outside of the CSR." 2. Time to pain progression (TTPP) section updated to describe modification to classification of responses. 3. Section 3.2.4 had minor changes to table numbers. 4. Section 3.3.1 had minor changes to table numbers. 5. Added the following text in section 3.3.4 for clarification: "The unconfirmed complete or partial response will be present as supportive information." 6. CCI [redacted] 7. CCI [redacted] 8. Reference to subgroup analysis was removed. 9. The following text was removed as per decision to not conduct this analysis:

		"Duration of response will be analysed for Arm B in the same manner as rPFS if the number of participants with DOR allows (but without the subgroup analysis). In addition, Swimmer plots will be produced. The bars in the swimmer plots indicate the duration of response for each participant, the y-axis indicates the participant ID." 10. Section 4.2.2.5 Prostate-specific antigen (PSA) response removed "The percent change from baseline in PSA levels at 12 weeks" due to decision to not conduct this analysis . 11. Section 4.2.3.1 "FACT-P compliance (overall compliance and by visit compliance) will be summarised for Arm B." was removed due to decision to not conduct this analysis 12. There are BPI-SF outputs which were deleted due to the decision to not conduct this analysis The text in section 4.2.3.2 BPI-SF updated accordingly. 13. There are Pharmacokinetic outputs which were deleted due to decision to not conduct this analysis. The text in section 4.2.5 Pharmacokinetics data was updated accordingly.

LIST OF ABBREVIATIONS

The following abbreviations and special terms are used in this Statistical Analysis Plan.

Abbreviation / Acronym	Definition / Expansion
AJCC	American Joint Committee on Cancer
AE	Adverse event
AESI	Adverse Event of Special Interest
AUC	Area under the curve
BMI	Body Mass Index
BoR	Best objective response
BPI-SF	Brief Pain Inventory – Short Form
CI	Confidence interval
CRF	Case Report Form
CR	Complete response
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
DOR	Duration of Response
DCO	Data cut-off
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
EWB	Emotional well-being
FACIT	Functional assessment of chronic illness
FACT-P	Functional Assessment of Cancer Therapy-Prostate
FAPSI-6	FACT Advanced Prostate Symptom Index-6
FAPSI-8	FACT Advanced Prostate Symptom Index-8
FWB	Functional wellbeing
HRQL	Health-Related Quality of Life

Abbreviation / Acronym	Definition / Expansion
CCI	[redacted]
ICF	Informed consent form
IV	Intravenous
LD	Longest diameter
mCRPC	Metastatic castrate-resistant prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NA	Not available
NED	No evidence of disease
NTL	Non-target lesion
OAE	Other significant adverse events
ORR	Objective response rate
PCS	Prostate Cancer Symptoms
PD	Progressive disease
PK	Pharmacokinetics
PO	*Per os* (orally)
PSA	Prostate-specific antigen
PR	Partial response
PRO	Patient reported outcomes
PT	Preferred Term
PWB	Physical well-being
QD	Take once every day
Q3W	Once every 3 weeks
Q4W	Once every 4 weeks
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumours
RP2D	Recommended Phase 2 dose
rPFS	Radiographic progression free survival

Abbreviation / Acronym	Definition / Expansion
sd	Standard deviation
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
SOC	System Organ Class
SRC	Safety Review Committee
SWB	Social well-being
TBL	Total Bilirubin
TL	Target lesion
TLF	Tables, listings and figures
TOI	Trial Outcome Index
TTPP	Time to pain progression

1 STUDY DETAILS

The exploratory analysis of this study will not form part of the Clinical Study Report (CSR) and are outside of the scope of this Statistical Analysis Plan (SAP).
The analyses described in this SAP are based upon the following study documents:

- Study Protocol, Version 3.0 (24 Nov, 2020)
- electronic Case Report Form (eCRF), Version 3.0 (05 Nov, 2020)

1.1 Study Objectives

Table 1 Study objectives	
Objectives	**Endpoints/Variables**
Primary	
• To determine the efficacy (as assessed by radiographic progression free survival [rPFS]) of AZD4635 plus durvalumab and separately of AZD4635 plus durvalumab plus cabazitaxel in participants with mCRPC.	• rPFS, defined as the time from first dose to radiographic progression as assessed by the Investigator per Response Evaluation Criteria in Solid Tumours (RECIST v1.1) (soft tissue) and Prostate Cancer Working Group 3 criteria (PCWG3) (bone) or death from any cause, whichever occurs first.
Secondary	
• To evaluate the safety and tolerability of each treatment regimen in participants with mCRPC.	• Physical examination, laboratory values (haematology, clinical chemistry, urinalysis, and tests for coagulation), vital signs, and electrocardiograms (ECGs). • Adverse events/serious adverse events (AEs/SAEs) collected throughout the study, from the time of the informed consent form signature through to the last safety follow-up visit.
• To determine the efficacy of AZD4635 plus durvalumab and separately of AZD4635 plus durvalumab plus cabazitaxel by assessment of overall survival (OS) in participants with mCRPC.	• OS, defined as the time from first dose until death due to any cause regardless of whether the participant withdraws from study treatment or receives another anti-cancer therapy.
• To determine the efficacy of AZD4635 plus durvalumab and separately of AZD4635 plus durvalumab plus cabazitaxel, by assessment of objective response rate (ORR) in participants with mCRPC.	• Confirmed ORR, defined as the proportion of participants with a confirmed CR or PR using overall radiographic response assessed by RECIST v1.1 and PCWG-3 criteria (bone), and will be based on a subset of all treated participants with measurable disease at baseline per the site Investigator.
• To determine the efficacy of AZD4635 plus durvalumab and separately of AZD4635 plus durvalumab plus cabazitaxel by assessment of duration of response (DoR) in participants with mCRPC.	• DoR, defined as the date of first documented response (which is subsequently confirmed) until the date of documented progression or death in the absence of disease progression.

• To determine the efficacy of AZD4635 plus durvalumab and separately ofAZD4635 plus durvalumab plus cabazitaxel by assessment of prostate-specific antigen (PSA) response in participants with mCRPC.	• Confirmed PSA_{50} response, defined as the proportion of participants achieving a ≥ 50% decrease in PSA from baseline to the lowest post-baseline PSA, confirmed by a consecutive PSA at least 3 weeks later and will be based on PSA evaluable participants (dosed participants with an abnormal baseline PSA [≥ 1 ng/mL]).
• Investigate the pharmacokinetics (PK) of AZD4635 when given in combination with durvalumab, and when given in combination with durvalumab plus cabazitaxel.	• AZD4635, durvalumab and cabazitaxel plasma concentration and derived PK parameters, where deemed appropriate.
• To determine the efficacy of AZD4635 plus durvalumab plus cabazitaxel in participants with mCRPC, by adenosine (ADO) signalling gene expression in high and low subgroups.	• rPFS, defined as the time from first dose to radiographic progression, assessed by the Investigator per RECIST 1.1 (soft tissue) and PCWG3 criteria (bone) or death from any cause, whichever occurs first by gene expression subgroup.
• To determine the effects of AZD4635 plus durvalumab and separately of AZD4635 plus durvalumab plus cabazitaxel on pain and other prostate cancer-related symptoms.	• Change from baseline in worst pain, average pain and pain interference in the daily activities scales of the BPI-SF. • Time to pain progression based on BPI-SF Item 3 "pain at its worst in the last 24-hours". • Change from baseline in the FAPSI-6 as derived from 6 items and the FAPSI-8 as derived from 8 items within the FACT-P, and the PCS, as derived from the 12 items in the prostrate-specific module of the FACT-P.
Exploratory	
• CCI [redacted]	• CCI [redacted]
• CCI [redacted]	• CCI [redacted]
• CCI [redacted]	• CCI [redacted]
• CCI [redacted]	• CCI [redacted]

1.2 Study Design

This is a Phase II, international, open-label, two-arm, non-randomised study of AZD4635 in participants with mCRPC. The primary objective is to determine the rPFS of AZD4635 plus durvalumab (Arm A) and separately of AZD4635 plus durvalumab plus cabazitaxel (Arm B) (See Figure 1). Participants in each arm will be stratified by the presence of measurable soft tissue metastasis (per RECIST v1.1, Protocol Appendix F) or bone-only metastasis (per Prostate Cancer Working Group 3 [PCWG3 criteria, Protocol Appendix H]). There will be no formal comparisons between treatment arms. Secondary endpoints include; safety, OS, confirmed ORR, DoR, confirmed PSA50 response, time to pain progression, and pharmacokinetics (PK).

AZD4635 plus durvalumab (Arm A) will consist of participants with mCRPC previously treated with one or more approved NHAs (eg, abiraterone acetate, enzalutamide, apalutamide and/or darolutamide), and one or more taxanes, or participants who are taxane ineligible (See Figure 1). As of November 2020, the Sponsor stopped enrolment in Arm A following decisions at the program level, not related to any safety issues. Ongoing participants in Arm A may continue treatment as planned (ie, as long as they receive clinical benefit and do not meet any discontinuation criteria).

AZD4635 plus durvalumab plus cabazitaxel (Arm B) will consist of 80 participants with mCRPC previously treated with docetaxel and one prior NHA (either abiraterone acetate or enzalutamide but not both (prior apalutamide is not allowed in Arm B).

Eligible participants must have histologically diagnosed mCRPC with no evidence of small cell histology, have had progression of disease ≤6 months prior to study entry (either by RECIST v1.1 or bone lesions per PCWG3) and ongoing androgen deprivation with serum testosterone <50 ng/mL.

Participants will be allocated to one of the following treatment arms:
Arm A: AZD4635 ([CCI] mg PO daily) plus durvalumab (1500 mg IV every 4 weeks [Q4W])
Note: As of November 2020, the Sponsor stopped enrolment in Arm A following decisions at the program level, not related to any safety issues.

Arm B: AZD4635 ([CCI] mg PO daily) plus durvalumab (1500 mg IV Q3W) plus cabazitaxel (20 or 25 mg/m2 IV Q3W as per local prescribing guidelines) (n=80)

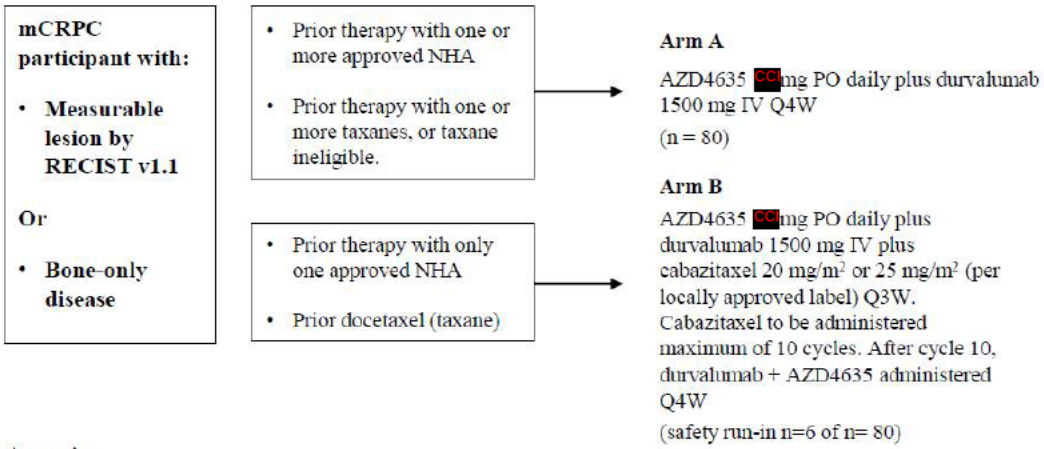
Cabazitaxel will be administered for a maximum of 10 cycles. After cycle 10 durvalumab + AZD4635 will be administered Q4W to harmonise with the Arm A treatment cycle length.

An archival tumour sample is required or the participant must be willing to undergo a baseline tumour biopsy. The collection of paired tumour biopsies will be requested during the study, however this is optional.

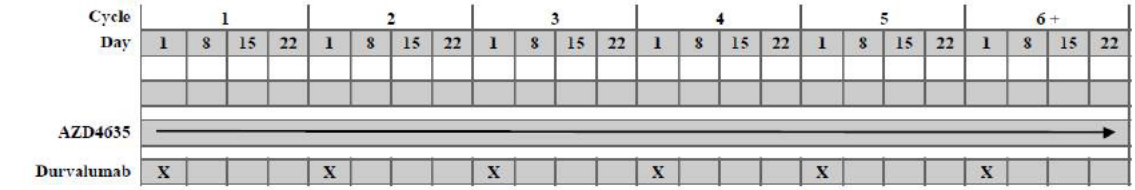
Participants in Arm A (AZD4635 plus durvalumab) will have disease assessments/imaging at baseline and every 8 weeks (± 7 days) from the start of dosing for the first 24 weeks and then every 12 weeks (± 7 days) thereafter (see Appendix A). Note: As of November 2020, the Sponsor stopped enrolment in Arm A. Ongoing participants in Arm A may continue treatment as planned (ie, as long as they receive clinical benefit and do not meet any discontinuation criteria).

Participants in Arm B (AZD4635 plus durvalumab and cabazitaxel) will have disease assessments/imaging every 9 weeks (± 7 days) from the start of dosing for the first 27 weeks and then every 12 weeks (± 7 days) thereafter (see Appendix B). A safety assessment to determine the safety and tolerability of this combination will be conducted by the Safety Review Committee (SRC) once the first 6 participants have completed a run-in period of at least 1 cycle (see section 5).

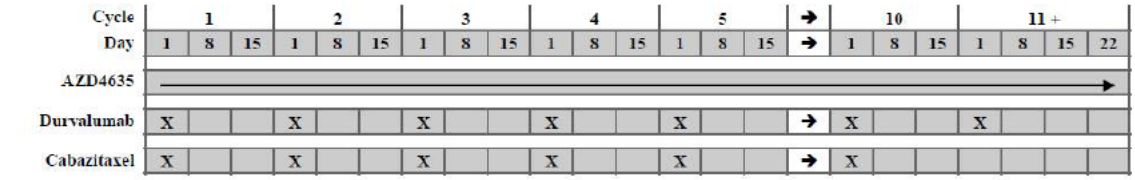
Figure 1 Study design



Arm A



Arm B



Note: As of November 2020, the Sponsor stopped enrolment in Arm A. Ongoing participants in Arm A may continue treatment as planned (ie, as long as they receive clinical benefit and do not meet any discontinuation criteria).

1.3 Number of Participants

As of November 2020, the Sponsor stopped enrolment in Arm A following decisions at the program level.

For Arm B, approximately 80 participants will be allocated to AZD4635 plus durvalumab plus cabazitaxel at the recommended Phase 2 dose (RP2D).

The primary efficacy endpoint is rPFS. It is anticipated that the study accrual period will be approximately 14 months for Arm B. CCI [redacted]

CCI [redacted]

CCI [redacted]

Eighty participants per arm will provide an estimate of the median rPFS. Confidence intervals (CI) will be constructed around the median rPFS, to enable decisions to be made about the likely success of future studies in this population.

CCI [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

A futility interim analysis will be carried out as described in the section 6.

2 ANALYSIS SET

2.1 Definition of Analysis Sets

All participants who received at least one dose of study treatment will be included in the safety analysis set. For the safety analysis, participants will be classified according to the treatment they actually received. For the efficacy analysis, participants will be classified according to the planned treatment. For the PK, baseline and demography analysis, participants will be classified according to the actual treatment.

Details of the analysis sets are presented in

Table **2** and *minimum safety evaluation: participants have both baseline of ECG and lab and have one of post-baseline from any domains among AE, ECG and lab.

**75% is out of dose in mg, not out of days.

Table 3.

Table 2 Analysis Sets

Analysis Set	Definition
Full analysis set (FAS)	All participants who received at least one (non-zero) dose of study treatment.
Evaluable for Efficacy	Dosed participants with a baseline tumour assessment.
Tumour response evaluable	Dosed participants with a baseline tumour assessment, and measurable disease at baseline.
Safety	All participants who received at least one (non-zero) dose of study treatment.
Dose-limiting toxicity (DLT) evaluable	A DLT evaluable participant is defined as the first 6 participants who has received AZD4635 in Arm B and either: • Has completed minimum safety evaluation requirements * and has received at least 75% of the specified AZD4635 doses of treatment concomitantly with durvalumab and cabazitaxel** during Cycle 1. Or • Has experienced a DLT during Cycle 1, the DLT evaluation period, for Arm B.
PSA Evaluable	Dosed participants with an abnormal baseline PSA (≥1ng/mL).
Pharmacokinetics (PK)	All participants who received at least 1 dose of study treatment with at least 1 reportable PK concentration.
Interim tumour response evaluable	• All dosed participants who had measurable disease at baseline and who had first dose at least 19 weeks prior to data extract of interim analysis.
Interim PSA evaluable	• All dosed participants with an abnormal baseline PSA (≥1ng/mL) and who had first dose at least 85 days prior to data extract of interim analysis.

*minimum safety evaluation: participants have both baseline of ECG and lab and have one of post-baseline from any domains among AE, ECG and lab.
**75% is out of dose in mg, not out of days.

Table 3 Summary of outcome variables and analysis sets

Outcome variable	Analysis Sets
Demography and baseline characteristics	Safety
Safety data	
Exposure	Safety
Adverse Events	Safety
Laboratory measurements	Safety
Vital Signs/ECG/Physical examination	Safety
Concomitant medications	Safety
Efficacy Data	
Best Objective Response	Tumour response evaluable and Evaluable for Efficacy Interim tumour response evaluable
Duration of Response	Tumour response evaluable **
rPFS	Evaluable for Efficacy
PSA	PSA Evaluable Interim PSA evaluable analysis set*
OS	FAS
PRO, BPI-SF and FACT-P	FAS
Pharmacokinetics	
Plasma Pharmacokinetic variables	PK

*Interim tumour response evaluable analysis set and interim PSA evaluable analysis set only apply in interim analysis.
**Duration of response will be analysed based on the subset of participants with confirmed response.

2.2 Protocol Deviations

Important protocol deviations (IPDs) are defined as a subset of protocol deviations that may significantly affect the completeness, accuracy, and/or reliability of the study data or that may significantly affect a patient's rights, safety, or well-being. The following general categories may be considered important protocol deviations:

Participants who deviate from key entry criteria per the Clinical Study Protocol (CSP) (Deviation 1) as below:

- Participants must have prostate cancer with histological confirmation [Inclusion criteria 2 of core CSP]
  - Disease must be metastatic and inoperable and for which there is no curative intervention available. Participants may have bone-only disease.

- Participants presenting with treatment-emergent neuroendocrine differentiation, but not primary small-cell features, are eligible.

- Known castrate-resistant disease, defined as [Inclusion criteria 3 of core CSP]:

  - Testosterone level in the castration range (levels <50 ng/dl) because of a previous, and ongoing, androgen-deprivation with luteinizing hormone-releasing hormone (LHRH) agonists or antagonists or bilateral orchiectomy. Participants must have developed progression of metastases following surgical castration or during medical androgen ablation therapy. Participants receiving medical castration therapy with gonadotropin-releasing hormone (GnRH) analogues should continue this treatment during this study.

- Evidence of disease progression ≤6 months defined by one or more of the following [Inclusion criteria 4 of core CSP]:

  - Progression as defined by RECIST v1.1 criteria for assessment of malignant soft tissue disease and lymph nodes

  - Progression of bone lesions on bone scan from a previous or baseline assessment per PCWG3

  - Rising PSA defined as at least two consecutive rises in PSA to be documented over a reference value (measure 1) taken at least 1 week apart.

- Must have measurable disease [Inclusion criteria 5 of core CSP]:

  - At least 1 documented lesion on either a bone scan or a computed tomography (CT)/magnetic resonance imaging (MRI) scan that can be followed for response is suitable for repeated measurement

  Or

  - Non-measurable disease must have measurable PSA ≥ 1.0 ng/mL as the minimum starting level for trial entry if the confirmed rise is the only indication of progression (excluding small cell carcinoma)

Additional Inclusion Criteria Specific for Arm A

- Participants in Arm A must have received the following prior therapy [Inclusion criteria 10 of core CSP]:
  - Maximum of 3 lines of therapy in the mCRPC setting
  - Prior therapy with one or more NHAs (eg, abiraterone acetate, enzalutamide, apalutamide, darolutamide) in either hormone-sensitive or hormone-refractory settings
  - Prior therapy with one or more lines of taxanes (eg, docetaxel and/or cabazitaxel)
  - Alternatively, must be taxane-ineligible
  - Prior therapy can be in either the hormone-sensitive or the hormone-refractory setting

Additional Inclusion Criteria Specific for Arm B

- Participants in Arm B must have received the following prior therapy [Inclusion criteria 12 of core CSP]:

- Prior docetaxel (taxane) in either hormone-sensitive or hormone-refractory settings
- Received no prior cytotoxic chemotherapy other than docetaxel for prostate cancer except for estramustine and except adjuvant/neo-adjuvant treatment completed >3 years ago.
- Prior therapy with only one NHAs (eg, abiraterone acetate or enzalutamide; prior apalutamide is not permitted) for treatment of mCRPC in either hormone-sensitive or hormone-refractory settings.
- Be suitable to receive concomitant GCSF during all cycles of cabazitaxel.

- Participants who meet the key exclusion criteria per the CSP (Deviation 2) as below [Exclusion criteria 7 of core CSP]:
  - Prior exposure to immune-mediated therapy including, but not limited to anti-CTLA-4, anti-PD-1, anti-PD-L1 and anti-PD-L2 antibodies, excluding therapeutic anti-cancer vaccines.

- Participants who meet the key exclusion criteria per the CSP (Deviation 3) as below [Exclusion criteria 9 of core CSP]:
  - Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc]). The following are exceptions to this criterion:
    - Participants with vitiligo or alopecia
    - Participants with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement
    - Any chronic skin condition that does not require systemic therapy
    - Participants without active disease in the last 5 years may be included but only after consultation with the Study Physician
    - Participants with coeliac disease controlled by diet alone

- Participants assigned to treatment who received their assigned study treatment at an incorrect dose more than 10% of the time or received an alternative study treatment to that which they were assigned (Deviation 4)

- Persistently missing important protocol required safety assessments (haematology, liver function test, chemistry panel and/or as per medical monitor discretion) and potentially having major impact to patient safety (clinical review on a case by case base) (Deviation 5).

- Baseline RECIST or Bone scan >28 days before start of assigned treatment (unless agreed with medical team), or no baseline RECIST 1.1 assessment on or before start of treatment and/or no baseline bone scan assessment on or before start of treatment (Deviation 6).

- Participant received study treatment but post-baseline tumour assessment scans not performed at all or major issues with scans not being performed in accordance with the protocol (Deviation 7).

- Participant received prohibited other anti-cancer therapy during study treatment period (Deviation 8).

- Changes to the procedures that impact the quality of the data or any circumstances that can alter the evaluation of the PK (Deviation 9).

- Met study treatment discontinuation criteria but continued study treatment and potentially had major impact to participants' safety according to clinical judgement (Deviation 10).

- Missed visits, assessments, or treatments that, in the opinion of the principal investigator, were due to the COVID-19 global pandemic and there was a significant effect on EITHER completeness, accuracy, and/or reliability of the participant's data, OR the participant's rights, safety or well-being (Deviation 11).

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

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

A list of all protocol deviations, including those reported by monitors, will be reviewed and decisions regarding how to handle these deviations will be documented by the study team physician, clinical pharmacology scientist and statistician prior to database lock. The final classification will be made prior to database lock. Important protocol deviations and any action to be taken regarding the exclusion of participants or affected data from specific analyses are defined in the project-specific Protocol Deviation Specification.

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

3 PRIMARY AND SECONDARY VARIABLES

3.1 General principles

Baseline measurements and change from baseline variables

Baseline will be the last non-missing value obtained prior to the first dose/administration of study medication and any information taken after first dose/administration of study medication will be regarded as post baseline information. If two visits are equally eligible to assess participant status at

baseline (e.g., screening and baseline assessments both on the same date prior to first dose/administration with no washout or other intervention in the screening period), the average should be taken as the baseline value. For non-numeric laboratory tests (i.e., some of the urinalysis parameters) where taking an average is not possible, then the clinical favourite value would be taken as baseline (i.e., normal and abnormal were observed on the same date prior to first dose/administration, then normal is considered as baseline value). In the scenario where there are two assessments on Day 1 prior to the first dose, one with time recorded and the other without time recorded, the one with time recorded would be selected as baseline, regardless of value normal/abnormal. For assessments on the day of first dose where time is not captured, a nominal pre-dose indicator, if available, will serve as sufficient evidence that the assessment occurred prior to first dose. 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 variables will be calculated as the post treatment value minus the value at baseline. For % change from baseline, calculate:

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

Study day will be calculated as:

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

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

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

Time Windows

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

For visit specific efficacy outputs, a windowing rule will be applied and will follow the protocol allowed visit window.

The following conventions should apply for safety and Patient reported outcomes (PRO):

- Inclusion within the time window should be based on the actual date and not the intended date of the visit.
- All unscheduled visit data should have the potential to be included in the summaries.
- For summaries showing the maximum or minimum values at a visit, the maximum/minimum value recorded on treatment at that visit (including within the corresponding window) will be used (regardless of where it falls in a window).
- Listings should display all values contributing to a time point for a participant.

- For visit based summaries, if there is more than one value per participant within a time window then the closest value to the scheduled visit date should be summarised, or the earlier, in the event the values are equidistant from the planned visit date.
- The listings should highlight the value for the participant that contributed to the summary table, wherever feasible.
- Note: in summaries of extreme values all post baseline values collected are used including those collected at unscheduled visits regardless of whether or not the value is closest to the scheduled visit date.
- For summaries at a participant level, all values should be included, regardless of whether they appear in a corresponding visit based summary, when deriving a participant level statistic such as a maximum.

End of Study Definition

The end of the study is defined as the last scheduled visit or contact of the last participant enrolled in the study. A participant is considered to have completed the study when he has completed his last scheduled visit or contact. The DCO for the primary analysis will occur when approximately 60% of the participants have progressed or died in Arm B. Data analysis will be performed and a CSR will be written based on this dataset. Following the decision to stop enrolment in Arm A, data from Arm A and Arm B will be reported in the same CSR when the DCO is reached for Arm B. If required, an additional analysis of OS for Arm B at a later DCO may be conducted and a CSR addendum written based on this dataset. In this case, more limited data collection for survival, study drug dosing and subsequent cancer therapy for Arm B will continue until that time according to the scheduled contact. SAEs will be collected. The clinical study database will be closed to new data after the DCO for the final analysis.

Following the primary DCO, any participants still receiving the investigational product (IP) at the time of DCO will be allowed to continue to receive the IP while deriving clinical benefit. Such participants will continue to be monitored for all SAEs up to 30 days after the last dose of IP or 90 days if participant is receiving the IP combined with durvalumab.

Outputs Display

The tables, listings and figures (TLF) shells will be followed to create the tables, listings and figures. The actual treatment group will be used for all safety analysis in this study. For all efficacy analysis, planed treatment group will be used. In the outputs, the following label of each arm will be used.

	Treatment label to display in TLF
Arm A	Arm A AZD4635 [CC] mg QD + durvalumab 1500mg Q4W
Arm B	Arm B AZD4635 [CC] mg QD +

	durvalumab 1500mg Q3W + cabazitaxel 20 or 25 mg/m2 Q3W

Note: Arm A data will only be listed and won't display in any summary tables.

3.2 Derivation of RECIST Visit Response

For all participants with measurable and non-measurable disease at baseline, 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 and also their best objective response to study treatment.

Baseline radiological tumour assessments are to be performed no more than 28 days before the start of study treatment and ideally as close as possible to the start of study treatment. The first follow-up assessment should be at Week 8 (Arm A) or Week 9 (Arm B). In Arm A follow-up assessments should be every 8 weeks ±1 week, from the start of dosing, for the first 24 weeks and then every 12 weeks (±1 week) thereafter. In Arm B follow-up assessments should be performed every 9 weeks ±1 week, from the start of dosing, for the first 27 weeks and then every 12 weeks (±1 week). Any other sites at which new disease is suspected should also be adequately imaged at follow-up.

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 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, non-CR/non-PD, or PD, using the information from TLs, NTLs and new lesions and depending on the status of their disease compared with baseline and previous assessments. If a 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).

Please refer to Table 4 below for the definitions of CR, PR, SD and PD.

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

3.2.1 Target lesions (TLs)

Measurable disease is defined as having at least one measurable lesion, not previously irradiated, which is ≥ 10 mm in the longest diameter (LD) (except lymph nodes which must have short axis ≥ 15 mm) with CT or 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/or the absence/presence of new lesions (see Table 4) for further details). If a participant does not have measurable disease at baseline then the TL visit response will be not applicable (NA).

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

Table 4 TL Visit Responses (RECIST 1.1)

Visit Responses	Description
Complete response (CR)	Disappearance of all target lesions since baseline. Any pathological lymph nodes selected as target lesions must have a reduction in short axis to < 10 mm.
Partial response (PR)	At least a 30% decrease in the sum of the diameters of TL, taking as reference the baseline sum of diameters.
Progressive disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm..
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
Not evaluable (NE)	Only relevant if any of the target lesions were not assessed or not evaluable or had a lesion intervention at this visit. Note: If the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a target lesion response.
Not applicable (NA)	No TLs are recorded at baseline.

Rounding of TL data

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

Missing TL data

For a visit to be evaluable then 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
- A 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 ≥ 5mm, from nadir even assuming the non-recorded TLs have disappeared

Lymph nodes

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

TL visit responses subsequent to CR

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

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

TL too big to measure

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

TL too small to measure

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

Irradiated lesions/lesion intervention

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

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

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

Step 2: If there was no evidence of progression after step 1, treat the lesion diameter (for those lesions with intervention) as missing and if □ 1/3 of the TLs have missing measurements then scale up as described in the 'Scaling' section below. If the scaling results in a visit response of PD then the 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 <10mm for lymph nodes) and the lesions that have been subject to intervention also have a value of 0 (or <10mm for lymph nodes) recorded. If scaling up is not appropriate due to too few non-missing measurements then the visit response will be set as NE.

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

Scaling

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

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

Example of Scaling

Lesion	Longest diameter (mm) at nadir visit	Longest diameter (mm) at follow-up visit
1	16	18
2	14	16
3	14	16
4	18	18
5	12	Intervention
Sum	**74**	**68**

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

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

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

$$68 \times 74 / 62 = 81 \text{ mm}$$

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

Lesions that split in two

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

Lesions that merge

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

Change in method of assessment of TLs

CT, MRI and clinical examination are the only methods of assessment that can be used within a trial, with CT and MRI being the preferred methods and clinical examination only used in special

cases. If a change in method of assessment occurs between CT and MRI this will be considered acceptable and no adjustment within the programming is needed.

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

3.2.2 Non-Target Lesions (NTLs) and new lesions

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

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

To achieve 'unequivocal progression' on the basis of NTLs, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in TLs, the overall 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.

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.

Table 5 NTL Visit Responses

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

3.2.3 Overall visit response – site investigator data

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

Table 6 Overall visit responses soft tissue response

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**

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

(NED = no evidence of disease)

3.2.4 Bone Lesion Progression using PCWG3

Bone lesions will be assessed by bone scan and will not be part of the RECIST v1.1 malignant soft tissue assessment. If more than one baseline scan is recorded then the measurement closest to but prior to date of first dose will be used.

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:

- First visit after baseline (expected Week 8 /Arm A and Week 9 /Arm B):
  Two or more new lesions are observed on the first scan after baseline compared to the baseline assessment. The confirmatory scan, performed at least 8/9 weeks later, must show two or more additional new metastatic bone lesions (for a total of four or more new bone lesions since the baseline assessment) for progression to be documented.
- From the 2nd visit onwards post-baseline:
  Two or more new lesions are observed on the first scan after baseline compared to the baseline assessment. The confirmatory scan, performed at least 8/9 weeks later, 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.

When progression is confirmed, the date of progression is the date of the earlier of the two scans used to confirm progression.

Table provides the definitions for the visit bone progression status for bone lesions.

Table 7 Bone progression status

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 progression.
Progressive Disease (PD)	Bone lesions fulfilling the requirements for at least 2 new lesions and confirmation of progression.
Not Evaluable (NE)	No evaluable follow-up bone scan

No Evidence of Disease (NED)	No Evidence of Disease.

3.3 Efficacy Variables

3.3.1 Radiological progression-free survival (rPFS)

rPFS, defined as the time interval from the first dose of AZD4635 until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the participant withdraws from treatment or receives another anti-cancer therapy prior to progression. Participants who have not progressed (defined as CR, PR or SD by RECIST v1.1 for soft tissue disease, or non-PD for bone disease) at the time of analysis will be censored at the time of the last evaluable RECIST v1.1 assessment or bone scan.

Participants who have not progressed (defined as CR, PR or SD by RECIST v1.1 for soft tissue disease, or non-PD for bone disease) or have not died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST assessment or bone scan. However, if the participant progresses or dies after two or more missed radiologic visits, the participant will be censored at the time of the latest evaluable RECIST 1.1 or bone scan assessment prior to the two missed visits.

Arm A:

Given the scheduled visit assessment scheme (every 8 weeks for the first 24 weeks and then every 12 weeks thereafter) the definition of 2 missed visits will change.

1. If the previous RECIST assessment is <= study day 49 (i.e. week 7) then two missing visits will equate to 17 weeks since the previous RECIST assessment, allowing for a late visit (i.e. 2 x 8 weeks + 1 week for a late assessment = 17 weeks).
2. If the previous RECIST assessment is >49 and < study day 106 (i.e. week 15) then two missing visits will equate to 18 weeks since the previous RECIST assessment, allowing for early and late visits (i.e. 2 x 8 weeks + 1 week for an early assessment + 1 week for a late assessment = 18 weeks).
3. If the two missed visits occur over the period when the scheduled frequency of RECIST assessments changes from eight-weekly to twelve-weekly this will equate to 22 weeks (i.e. take the average of 8 and 12 weeks which gives 10 weeks and then apply same rationale, hence 2 x 10 weeks + 1 week for an early assessment + 1 week for a late assessment = 22 weeks). The time period for the previous RECIST assessment will be from study days 106 to 162 (i.e. week 15 to week 23).
4. From week 23 onwards (when the scheduling changes to twelve-weekly assessments), two missing visits will equate to 26 weeks (i.e. 2 x 12 weeks + 1 week for an early assessment + 1 week for a late assessment = 26 weeks).

Arm B:

Given the scheduled visit assessment scheme (every 9 weeks for the first 27 weeks and then every 12 weeks thereafter) the definition of 2 missed visits will change.

1. If the previous RECIST assessment is <= study day 56 (i.e. week 8) then two missing visits will equate to 19 weeks since the previous RECIST assessment, allowing for a late visit (i.e. 2 x 9 weeks + 1 week for a late assessment = 19 weeks).
2. If the previous RECIST assessment is >56 and < study day 120 (i.e. week 17) then two missing visits will equate to 20 weeks since the previous RECIST assessment, allowing for early and late visits (i.e. 2 x 9 weeks + 1 week for an early assessment + 1 week for a late assessment = 20 weeks).
3. If the two missed visits occur over the period when the scheduled frequency of RECIST assessments changes from nine-weekly to twelve-weekly this will equate to 23 weeks (i.e. take the average of 9 and 12 weeks which gives 10.5 weeks and then apply same rationale, hence 2 x 10.5 weeks + 1 week for an early assessment + 1 week for a late assessment = 23 weeks). The time period for the previous RECIST assessment will be from study days 120 to 183 (i.e. week 17 to week 26).
4. From week 26 onwards (when the scheduling changes to twelve-weekly assessments), two missing visits will equate to 26 weeks (i.e. 2 x 12 weeks + 1 week for an early assessment + 1 week for a late assessment = 26 weeks).

However, if the patient progresses or dies immediately after 2 or more consecutive missed visits for either soft tissue or bone assessments, the patient will be censored at the earliest of the previous RECIST 1.1 assessment (taking the latest target lesion, non-target lesion or new lesion scan date) or previous bone scan assessment prior to the two consecutive missed visits (if RECIST and bone scan done at different visits). Else the latest of the previous RECIST1.1 assessment and bone scan if done at the same visit. If the patient has no evaluable visits or does not have baseline data they will be censored at Day 1 unless they die within 2 visits of baseline (in which case their date of death will be used).

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

The following rules will be applied:

1 For investigational assessments, the date of progression will be determined based on the **earliest** of the dates of the component that triggered the progression

2 When censoring a participant for rPFS the participant will be censored at the latest of the dates contributing to a particular overall visit assessment.

Table provides the definitions how the visit responses for soft tissue (according to RECIST1.1

criteria) and bone progression status (according to PCWG3 criteria) are combined to give an overall radiological objective visit response.

Table 8 Overall visit responses

Overall visit soft tissue response (RECIST 1.1)[a]	Bone progression Status (PCWG3)[b]	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	Any	**Non-PD**
NED	NE	Any	**NE**
NE	Non-PD or NE	Any	**NE**
PD	Any	Any	**PD**
Any	PD	Any	**PD**

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable (if an assessment is missing, it will be considered NE), NED = No Evidence of Disease (only relevant if there were no TL and NTLs at all visits)
a See section 3.2.3.
b See section 3.2.4.

3.3.2 Overall survival (OS)

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

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

Note: Survival calls will be made in the week following the date of DCO for the analysis, and if participants are confirmed to be alive or if the death date is post the DCO date these participants will be censored at the date of DCO. If the last known alive status is before DCO, then minimum of [the last known alive date and date of DCO] will be used as censored date. The status of ongoing, withdrawn (from the study) and "lost to follow-up" participants at the time of the OS analysis should be obtained by the site personnel by checking the participant's notes, hospital records, contacting the participant's general practitioner and checking publicly-available death registries. In the event that

the participant has actively withdrawn consent to the processing of their personal data, the vital status of the participant can be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws.
Note that for any OS analysis performed in the absence of survival calls being made, it may be necessary to use all relevant CRF fields to determine the last recorded date on which the participant was known to be alive for those participants still on treatment. The last date for each individual participant is defined as the latest among the following dates recorded on the case report forms (CRFs):

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

3.3.3 Objective response rate (ORR)

For the secondary endpoint ORR assessed by RECIST 1.1 and PCWG3, only dosed participants with measurable disease (target lesions) at baseline will be included in the analysis. A participant will be classified as a responder if the RECIST 1.1 criteria for a CR or PR are satisfied (as well as the absence of confirmed progression on bone scan assessed by PCWG3). ORR is defined as the percentage of participants with a confirmed, programmatically determined CR or PR and will be based on a subset of all dosed participants evaluable for response with measurable disease at baseline per the site investigator assessed by RECIST v1.1 and PCWG-3 criteria (bone).

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 radiographic 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 (note that for this analysis radiotherapy is not considered a subsequent anti-cancer therapy) and then respond will not be included as responders in the ORR (i.e. both visits contributing to a response must be prior to subsequent therapy for the 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.

3.3.4 Best objective response (BoR)

Best objective response (BoR) is calculated based on the overall visit responses from each RECIST assessment, described in Section 3.2. It is the best response a participant has had following first dose but prior to starting any subsequent cancer therapy and up to and including RECIST progression or the last evaluable assessment in the absence of RECIST progression. Categorisation of BoR will be based on RECIST using the following response categories: CR, PR, SD, PD and NE.

CR or PR must be confirmed. For CR/PR, the initial overall visit assessment which showed a response will use the latest of the dates contributing towards a particular overall visit assessment. The unconfirmed complete or partial response will be presented as supportive information.

For determination of a best response of SD, the earliest of the dates contributing towards a particular overall visit assessment will be used. SD should be recorded for each arm as below:

> For **Arm A**: SD should be recorded at least 8 weeks minus 7 days, i.e. at least 49 days (to allow for an early assessment within the assessment window), after first dose/administration of study medication.
> For **Arm B**: SD should be recorded at least 9 weeks minus 7 days, i.e. at least 56 days (to allow for an early assessment within the assessment window), after first dose/administration of study medication.

It will be determined programmatically based on RECIST using all site investigator data up until the first progression event. The denominator will be consistent with that used in the ORR analysis.
For participants whose progression event is death, BoR will be calculated based upon all evaluable RECIST assessments prior to death.

For participants who die with no evaluable RECIST assessments:

> For **Arm A**: if the death occurs ≤ 119 days (i.e., 2 x 8 weeks + 7 days to allow for a late assessment within the assessment window) after first dose/ administration of study medication, then BoR will be assigned to the progression (PD) category. For participants who die with no evaluable RECIST assessments, if the death occurs > 119 days after start of treatment then BoR will be assigned to the NE category.
>
> For **Arm B**: if the death occurs ≤ 133 days (i.e., 2 x 9 weeks + 7 days to allow for a late assessment within the assessment window) after first dose/ administration of study medication, then BoR will be assigned to the progression (PD) category. For participants who die with no evaluable RECIST assessments, if the death occurs > 133 days after start of treatment then BoR will be assigned to the NE category.

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

3.3.5 Duration of Response (DoR)

Duration of response will be defined as the time from the date of first documented response (which is subsequently confirmed using RECIST v1.1) until date of documented progression or death in the absence of disease progression (ie, date of rPFS 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 rPFS 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 rPFS censoring date as the date at which that participant is censored for DoR.

3.3.6 Change in tumour size

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

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

Tumour size is the sum of the diameters 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, including the measurement occurring on the date of first dose/administration. The percentage change in target lesion tumour size at each visit for which data are available will be obtained for each participant taking the difference between the sum of the target lesions at each visit and the sum of the target lesions at baseline divided by the sum of the target lesions at baseline multiplied by 100 (i.e. (week x - baseline)/baseline * 100).

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

Whenever TL tumour size data for the week XX visit (Note: or visit at which progression was documented if before week XX) is available then this should be used in the analysis. A windowing rule will be applied and will follow the protocol allowed visit window; therefore any RECIST scan performed within ± 1 week of the protocol scheduled visit will be used for that visit.
If following the scaling up rules, best percentage change cannot be calculated due to missing data, and a participant has no post baseline assessments, then the following imputation rules should be applied:

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

- If there is no evidence of progression, assume that the data is missing completely at random, the participant will be excluded from the analysis.
- If it is known that the participant has died, impute a best percentage change from baseline as the maximum (i.e. corresponding to the biggest increase in TL tumour size) best percentage change reported on the study.

3.3.7 Prostate-specific antigen (PSA)

PSA response rate

PSA response rate is defined as the proportion of PSA evaluable participants achieving a ≥50% decline from baseline to the lowest post-baseline PSA results, confirmed by a second consecutive PSA assessment at least 3 weeks later. Ignore early rises (before 12 weeks) in determining PSA response. For patients who receive a subsequent anti-cancer therapy (note that for this analysis radiotherapy is not considered a subsequent anti-cancer therapy), data will only be included until the start date of the subsequent anti-cancer therapy.

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

PSA progression

If there is a PSA decline from baseline, progression is defined as the date of the first PSA increase that is both ≥25% and ≥2 ng/mL above the nadir and which is confirmed by a second value ≥ 3 weeks later, even if within 12 weeks. If there is no PSA decline from baseline, progression is defined as a ≥ 25% increase and ≥2 ng/mL increase from baseline beyond 12 weeks.

For patients who receive a subsequent anti-cancer therapy (note that for this analysis radiotherapy is not considered a subsequent anti-cancer therapy), data will only be included until the start date of the subsequent anti-cancer therapy.

Whenever PSA data for the week XX visit is available then this should be used in the analysis. A windowing rule will be applied and will follow the protocol allowed visit window; therefore any PSA assessment performed within ± 1 week of the protocol scheduled visit will be used for that visit.

3.4 Patient reported outcomes (PRO)

The patient reported outcome (PRO) instruments, a Brief Pain Inventory – Short Form (BPI-SF) (see Protocol Appendix J) and FACT-P (see Protocol Appendix K) will be administered to all participants. These two instruments will be used to assess pain and quality of life in study participants.

3.4.1 Functional assessment of cancer therapy – prostate cancer (FACT-P)

The FACT-P was developed to measure health related quality of life (HRQL) in men with prostate cancer. It consists of 4 subscales (physical, emotional, functional and social/family well-being) plus

a 12-item prostate-specific module, the Prostate Cancer Symptoms (PCS) subscale, which highlights concerns specific to participants with prostate cancer.

In addition, the FACT-P also supports the calculation of a trial outcome index (TOI) score (the sum of the physical wellbeing [PWB], functional wellbeing [FWB] and PCS scores), and the FACT Advanced Prostate Symptom Index-6 [FAPSI-6], a symptom score made up of 6 items from within the FACT-P (pain [n=3], fatigue [n=1], weight loss [n=1], and concerns about the condition getting worse [n=1]) and the FACT Advanced Prostate Symptom Index-8 [FAPSI-8], a symptom score made up of 8 items from within the FACT-P (pain [n=3], fatigue [n=1], weight loss [n=1], urinary conditions [n=2], and concerns about the condition getting worse [n=1]). CCI [redacted] The FACT-P will be measured at the times outlined in the schedule of activities (see Appendix A and Appendix B).

The following outcome measures will be calculated from the FACT-P questionnaire (see CSP Appendix K), the resulting value is the total score for the associated questions or scaled scores:

- Physical well-being subscale (PWB) (Questions GP1 to GP7)
- Social/family well-being subscale (SWB) (Questions GS1 to GS7)
- Emotional well-being subscale (EWB) (Questions GE1 to GE6)
- Functional well-being subscale (FWB) (Questions GF1 to GF7)
- Prostate cancer subscale (PCS) (Questions C2, C6, P1 to P8, BL2 and BL5)
- Trial Outcome Index (TOI), sum of PWB, FWB and PCS
- Functional Assessment of Prostate Cancer Symptoms Index 6 (FAPSI-6) (Questions P1 to P3, GP1, C2 and GE6)
- Functional Assessment of Prostate Cancer Symptoms Index 8 (FAPSI-8) (Questions P1 to P3, GP1, C2, P7, P8 and GE6)
- FACT-P total score (sum of scores of all the sub-scales: PWB, SWB, EWB, FWB and PCS)

Items to be reversed:

- Each question in the FACT-P questionnaires has a choice of 5 responses, "Not at all", "A little bit", "Somewhat", "Quite a bit" and "Very much". The scores range from 0 ("Not at all") to 4 ("Very much") for positively phrased questions. Negatively phrased questions have a reverse scoring, from 0 ("Very much") to 4 ("Not at all"). This results in a consistent approach, where higher scores indicate a better quality of life.
- Note, questions that are reversed (via subtraction of the response from 4) are: GP1-7, GE1, GE3-6, C2, P1-3, P6-P8 and BL2.

Missing data

As per the FACIT scoring guidelines (Cella et al 1993, Cella 1994, Esper et al 1997),

- More than 80% of questions in a questionnaire must be completed for the questionnaire to have the FACT-P total score evaluable. If 80% or less of questions are completed, the FACT-P total scores will not be calculated.

- For each domain (PWB, SWB, EWB, FWB and PCS) if more than 50% of the items were answered (e.g., a minimum of 4 of 7 items, 4 of 6 items, etc), the subscale score will be

calculated by multiplying the sum of subscale by the number of items in the subscale, then dividing by the number of items actually answered:

Subscale score= (sum of item scores x N of items in subscale)/ N of items answered

- If at least 50% of the domain items are missing, that domain will be treated as missing and thus NE. The total score for each variable (FACT-P TOI and FACT-P total) is then calculated as the sum of the un-weighted prorated scores. If a domain score is NE, any health related quality of life (HRQL) variable which these domains contribute to is also termed NE. For example, for the FACT-P TOI variable, if PWB is NE at a visit, the FACT-P TOI variable is also NE at this visit. Also, the FACT-P total score cannot be computed if any of the domain scores is NE.

Visit responses

The last non-missing assessment before first dose of study treatment will be assigned to be the baseline assessment. At each post-baseline visit, the following criteria as listed below in Table will be used to assign a visit response for the FACT-P total score, FACT-P TOI, FAPSI-6, PCS and FWB scores (Cella et al 2009). This response should be maintained for 2 consecutive visits.

Table 9 Definition of visit response for FACT-P, FACT-P TOI, FAPSI-6, PCS and FWB

Score	Change from baseline	Visit response
FACT-P total score	≥+10	Improved
	≤-10	Worsened/Deterioration
	Otherwise (ie, >-10 and <+10)	Stable/No change
	Missing/non-calculable score	Not evaluable
FACT-P TOI	≥+9	Improved
	≤-9	Worsened/Deterioration
	Otherwise (ie, >-9 and <+9)	Stable/No change
	Missing/non-calculable score	Not evaluable
FAPSI-6	≥+3	Improved
	≤-3	Worsened/Deterioration
	Otherwise (ie, >-3 and <+3)	Stable/No change
	Missing/non-calculable score	Not evaluable
PCS	≥+3	Improved
	≤-3	Worsened/Deterioration
	Otherwise (ie, >-3 and <+3)	Stable/No change
	Missing/non-calculable score	Not evaluable
FWB	≥+3	Improved
	≤-3	Worsened/Deterioration
	Otherwise (ie, >-3 and <+3)	Stable/No change
	Missing/non-calculable score	Not evaluable

1. TOI: trial outcome index: the sum of the physical wellbeing [PWB], functional wellbeing [FWB] and PCS scores.
2. FAPSI-6: a symptom score made up of 6 items from within the FACT-P.
3. PCS: a 12-item prostate-specific module, the Prostate Cancer Symptoms subscale of FACT-P.
4. FWB: functional wellbeing, the subscale of FACT-P

Note for some participants it will not be immediately possible to obtain a visit response for a particular subscale, for example:

- Participants with no baseline score for a particular subscale, or no baseline data at all.
- Participants whose baseline subscale score is too close to the maximum or minimum possible score to allow an increase or decrease of the specific size to be observed.

For participants whose baseline score is greater than the maximum possible score for that subscale minus the score needed to satisfy improvement, the best visit response possible will be "No Change".

For participants whose baseline score is less than the threshold needed for worsening (e.g., a baseline FACT-P TOI < 5) all post-baseline visit responses will be considered not-calculable.

For those participants who meet the criteria above (where it is not possible to improve or worsen), descriptive data will be provided.

At the conclusion of the study, the criteria listed in Table will be used to assign a best overall response score based on the individual visit responses.

Table 10 Best overall score response for FACT-P, FACT-P TOI, FAPSI-6, PCS and FWB

Overall score response	Criteria
Improved	Two consecutive visit responses of 'improved'. Consecutive visits need to be at least 3 weeks apart.
No change	Does not qualify for overall score response of 'improved'. Two consecutive visit responses of either 'no change', or 'improved' and 'no change'
Worsened	Does not qualify for overall score response of 'improved' or 'no change'. A visit response of 'worsened'
Other	Does not qualify for one of the above
Not evaluable	Missing or non-calculable scores

Time to deterioration for FACT-P

Time to deterioration in HRQL as measured by FACT-P total score will be defined as the interval from the date of first dose until the date of the first clinically meaningful deterioration that is confirmed at a subsequent visit at least 3 weeks apart with no improvement in between the visits (except if it was the participant's last available assessment) or death (by any cause) in the absence of a clinically meaningful deterioration, regardless of whether the participant discontinues study drug(s) or receives another anti-cancer therapy prior to the deterioration in FACT-P total score. Death will be included as an event only if it occurs within 2 PRO assessment visits from the last available PRO assessment. Time to deterioration as measured by FACT-P TOI, FAPSI-6, PCS and FWB will be derived similarly.

A worsening is as described in Table for example, for FACT-P TOI a decrease in score from baseline of ≥ 9, or "Subject too affected by symptoms of disease under investigation" answered as the reason for not completing HRQL at a post-baseline visit will constitute a deterioration. Improvement is also as defined within Table .

Radiologic progression or a reason for not completing the questionnaire of "Subject unwilling", "Subject too sick, other than disease under investigation" or "Administrative failure to distribute questionnaire to Subject" will not be considered as deterioration in symptoms.

Note, under the same principles applied to the primary outcome variable (rPFS), time to deterioration will be derived regardless of whether the participant withdraws from study treatment prior to symptom deterioration. A number of situations will lead to a participant's time to deterioration of HRQL endpoints being censored. These are:

- If a participant either dies or meets the criteria for deterioration after 2 or more missed HRQL assessments, then the participant will be censored at the time of the latest evaluable HRQL assessment. These participants will be presented as "Censored FACT-P Total Score" in summaries, same apply to FACT-P TOI, FAPSI-6, PCS and FWB.

- Participants who have not met the criteria for symptom deterioration or have not died at the time of analysis will be censored at the time of the latest evaluable HRQL assessment:
  - The censoring date will be the date of the last assessment that led to evaluable being assigned for FACT-P total score. These participants will be presented as alive and deterioration-free in summaries.

  - Participants with no evaluable baseline or post-baseline data will be censored at Day 1 unless they die within 2 visits of baseline. These participants will be presented as censored in summaries.

- Participants whose baseline subscale score is close to the minimum possible

  - For participants whose baseline score is less than the threshold needed for worsening (e.g., a baseline FACT-P TOI of < 6), time to deterioration will be censored at Day 1 unless they die within 2 visits of baseline. Participants who haven't died will be presented as "Censored FACT-P Total Score" in summaries, similar apply to FACT-P TOI, FAPSI-6, PCS and FWB.

The time to deterioration of HRQL will be derived based on assessment dates, not visit dates, unless the participant is too affected by symptoms of disease under investigation, in which case there are no assessment dates and visit dates will be used.

PRO compliance

Summary measures of overall compliance and compliance over time will be derived for FACT-P. These will be based upon the following definitions:

- Received form: a form that has been received and has a completion date and at least one individual item completed.
- Expected form: a form that is expected to be completed at a scheduled assessment time e.g. a form from a participant who has not withdrawn from the study at the scheduled assessment time but excluding participants in countries with no available translation. For participants that have progressed, the latest of progression and safety follow-up will be used to assess whether the participant is still under FACT-P follow-up at the specified assessment time. Date of study discontinuation will be mapped to the nearest visit date to define the number of expected forms.
- Evaluable form: a form with a completion date and at least one subscale that is non-missing.
- Completed questionnaire: a form with all questions completed.
- Overall FACT-P compliance rate is defined as the total number of evaluable forms across all time points, divided by total number of forms expected to be received across all time points multiplied by 100.

- Overall participant compliance rate is defined for each treatment group as the total number of participants with both an evaluable baseline and at least one evaluable follow-up form (as defined above), divided by the total number of participants expected to have completed at least a baseline FACT-P form multiplied by 100.

Compliance over time will be calculated separately for each visit, including baseline, as the number of participants with an evaluable form at the time point (as defined above), divided by number of participants still expected to complete forms at that visit. Similarly, the evaluability rate over time will be calculated separately for each visit, including baseline, as the number of evaluable forms (per definition above), divided by the number of received forms. Completion rate will be calculated separately for each visit, including baseline, as the number of completed questionnaires (per definition above), divided by the number of received questionnaires.

3.4.2 Brief pain inventory – short form (BPI-SF)

Worst pain (item 3), average pain (item 5) and pain's interference with daily life will be assessed during the study intervention using the (Brief Pain Inventory – Short Form) BPI-SF at the times outlined in the schedule of assessments. The BPI-SF comprises a total of 15 items measuring 2 domains: pain severity and pain interference. Items measuring pain severity (including 'worst pain') are rated on an 11-point numeric rating scale (NRS) ranging from 0=No pain to 10=Pain as bad as you can imagine. All BPI-SF items are measured using a 24 - hour recall period.

The following outcome measure will be calculated for the BPI-SF:

- Pain severity (Questions 3, 4, 5 and 6)
- Pain Interference (Question 9 A-G)

For each outcome measure the mean score of non-missing items will be calculated. For pain interference at least 50% of the items must have a response for a mean score to be calculated. The individual responses to the questions comprising the pain severity domain will also be summarised.

Absolute change in the BPI-SF pain and pain interference scores will be calculated as change from baseline at each clinic visit.

Visit response of BPI-SF worst pain intensity item (item 3)

The last non-missing assessment before first dose of study treatment will be assigned to be the baseline assessment. At each post-baseline visit, the following criteria as listed below in Table will be used to assign an individual visit response for worst pain. Proportion of participants with individual visit response as improved, stable, or deteriorated in worst pain intensity item compared to baseline at each time point will be summarised.

Table 11 Definition of individual visit response for worst pain

Score	Change from baseline	Visit response
Worst pain intensity item (item 3)	⩾+2	Worsened/Deterioration
	⩽-2	Improved
	Otherwise (ie, <2 and >-2)	Stable/No change
	Missing/non-calculable score	Not evaluable

BPI-SF item 3 pain severity at baseline

The follow criteria will use to calculate the proportion of participants with BPI-SF item 3 pain severity at baseline.

- No pain: Score of 0 on BPI-SF item 3
- Mild pain: Score of 1-3 on BPI-SF item 3
- Moderate pain: Score of 4-7 on BPI-SF item 3
- Severe pain: Score of 8-10 on BPI-SF item 3
- Missing data: No data available for scoring

Time to pain progression (TTPP)

Time to pain progression is defined as the time interval from the date of first dose to the first date a participant experienced an increase by ≥2 from baseline in the BPI-SF worst pain intensity item (item 3) observed at 2 consecutive evaluations ≥14 days apart. Participants who have not experienced pain progression at the time of analysis will be censored on the last known date when a participant was known to have not progressed. Participants with no on-study assessment or no baseline assessment will be censored at Day 1.

Note, under the same principles applied to time to deterioration for FACT-P, time to pain progression will be derived regardless of whether the participant withdraws from study treatment prior to pain progression. A number of situations will lead to a participant's time to pain progression endpoints being censored. These are:

- If a participant either meets the criteria for pain progressionafter 2 or more missed BPI-SP assessments, then the participant will be censored at the time of the latest evaluable BPI-SP assessment. These participants will be presented as "Progressed later" in summaries.
- Participants who have not met the criteria for pain progression or have died at the time of analysis will be censored at the time of the latest evaluable BPI-SP assessment:
  - The censoring date will be the date of the last assessment that led to evaluable being assigned for BPI-SF. These participants will be presented as alive and pain progression-free in summaries.
  - Participants with no evaluable baseline or post-baseline data will be censored at Day 1. These participants will be presented as censored in summaries.

The time to pain progression will be derived based on assessment dates, not visit dates, unless the participant is too affected by symptoms of disease under investigation, in which case there are no assessment dates and visit dates will be used.

PRO Compliance

Summary measures of overall compliance and compliance over time will be derived for the BPI-SF. These will be based upon the compliance derivations described for FACT-P.

3.5 Other variables

3.5.1 Prior, concomitant and post medications and therapies

All therapies (drug or non-drug), including herbal preparations, whether prescribed or over-the-counter, that are used during the study will be recorded in the eCRF. Details include generic and/or brand names of medications, WHO drug dictionary encoding, reason for use, route, dose, dosing frequency, and start and stop dates.

- Prior medications are those taken prior to study treatment with a stop date prior to the first dose of study treatment.
- Concomitant medications are those with a stop date on or after the first dose date of study treatment (and could have started prior to or during treatment). Medications with a start date after the last dose date of study treatment will not considered as concomitant medications.
- Post-treatment medications are those with a start date after the last dose date of study treatment.

Missing start and stop dates for medications will be imputed using the rules described in Section 4.2.1.7.

3.6 Safety variables

3.6.1 Exposure and dose interruptions

Duration of exposure is defined as:

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

Arm A: Total treatment duration of durvalumab = min (last dose date where dose > 0 +27, date of death, date of DCO) − date of first dose +1

Arm B: If death or DCO happened within the first 10 cycles: Total treatment duration of durvalumab = min (last dose date where dose > 0 +20, date of death, date of DCO) − date of first dose +1. If death or DCO happened after the first 10 cycles, Total treatment duration of durvalumab = min (last dose date where dose > 0 +27, date of death, date of DCO) − date of first dose +1

Arm B: If death or DCO happened within the first 10 cycles, the total treatment duration of cabazitaxel is as below, after the first 10 cycles, cabazitaxel will discontinue.

Total treatment duration of cabazitaxel= min (last dose date where dose > 0 +20, date of death, date of DCO) − date of first dose +1

2 Actual exposure = intended exposure – total duration of dose interruptions, where intended exposure will be calculated as above and a dose interruption is defined as any length of time where the participant has not taken any of the planned daily dose. Note the actual exposure only apply to AZD4635, as the total duration of dose interruption for cabazitaxel and durvalumab will not be calculated.

The actual exposure calculation makes no adjustment for any dose reductions that may have occurred.

Number of treatment cycles received

Exposure will also be measured by the number of cycles received for IV administered treatment. A cycle corresponds to a period of 28 days for Arm A, and 21 days for Arm B for the first 10 cycles and 28 days thereafter. If the last dose is in Cycle 1, the number of cycles received will be 1. If a cycle is prolonged due to toxicity, this should still be counted as one cycle. A cycle will be counted if treatment is started even if the full dose is not delivered.

Missed or forgotten doses

Missed and forgotten doses should be recorded on the Exposure AZD4635 form of CRF 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 Discontinuation of study drug AZD4635 will be used in the programming.

3.6.2 Dose intensity

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

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

3.6.3 Adverse events

Adverse events, including SAEs, will be collected from time of signature of ICF throughout the treatment period and including the 30-day and 90-day follow-up period. SAEs will be recorded from the time of signing of the informed consent form. Treatment emergent AE is defined as adverse events

with an onset date on or worsen after the date of first dose and up to and including 30 days following the date of last dose of AZD4635 or Cabazitaxel, whichever occur later, or adverse events with an onset date on or worsen after the date of first dose and up to and including 90 days following the date of last dose of Durvalumab. The Medical Dictionary for Regulatory Activities (MedDRA) (version 23.0 or higher) will be used to code the AEs. AEs will be graded according to the National Cancer Institute Common Terminology Criteria for AEs (CTCAE Version 5.0).

Other significant adverse events (OAE)

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

AEs of special interest (AESI)

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the Investigational Product and may require close monitoring. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this investigational product.
AESIs for durvalumab include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants and/or hormone replacement therapy.
AESIs of durvalumab have been identified as list of categories will be provided by the patient safety team prior to DBL.
More information regarding AESIs can be found in Appendix B5 of the protocol. Other categories may be added or existing terms may be modified as necessary. An AstraZeneca medically qualified expert after consultation with the Global Participant Safety Physician has reviewed the AEs of interest and identified which higher-level terms and which preferred terms contribute to each AESI. Further reviews may take place prior to DBL to ensure any further terms not already included are captured within the categories. Preferred terms used to identify AESI will be listed before DBL. Immune Mediated Adverse Events (imAE) is defined as a subset of AESI which consider interventions of corticosteroids, immunosuppressants, and/or endocrine therapy; are deemed consistent with having an immune-mediated mechanism of action and where there was no clear alternative etiology. Automated adjudication approach via programming will be applied to identify imAEs, and will be reported outside of the CSR.

3.6.4 ECG changes

Twelve-lead ECGs will be obtained after the participant has been resting supine for at least 10 minutes prior at times indicated in the screening and the treatment arm (See Appendix A and Appendix B). All ECGs should be recorded with the participant in the same physical position. Three ECG recordings are required during screening (≤14 days prior to Day 1), prior to the first dose of study drug intervention Cycle 1 Day 1, and at the EOT visit. For triplicate ECGs, the mean of the three ECG assessments will be used to determine the value at that time point. Baseline of ECG is the mean of

last three ECG assessments prior to first dose. If there are only two ECG assessments prior to first dose are available, then take the average of these last two ECG assessment prior first dose as baseline of ECG; if there are only one ECG assessments prior to first dose are available, then take the last one ECG assessment prior to first dose as baseline of ECG. For all ECGs, details of rhythm, PR, R-R, QRS and QT intervals and an overall evaluation will be recorded. For numeric ECG parameters, change from baseline in ECG variables will be calculated for each post-dose visit on treatment. During the study, clinically significant abnormal ECG findings not present at baseline should be reported as AEs (if present, the clinical signs and symptoms associated with the abnormal finding should be reported as the AE with the ECG abnormality given as explanatory information.

From these resting 12-lead ECGs values of the QT and RR intervals and the QT interval corrected for heart rate using Fridericia's correction (QTcF) is derived using the following formula:

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

The value of QTcF (msec) will be re-derived from the values of RR and QT during the creation of the reporting database.

3.6.5 Vital sign changes

Vital signs (resting heart rate, systolic and diastolic blood pressure, respiration rate, and body temperature), and height (at screening only) will be assessed at the times indicated in the treatment arm schedule of activities(Appendix A and Appendix B).
Change from baseline in vital signs variables will be calculated for each post-dose visit on treatment. During the study, clinically significant abnormal vital signs findings not present at baseline should be reported as an AE.

3.6.6 Laboratory data

See Table for the list of clinical safety laboratory tests to be performed, the screening tests, and the treatment arm schedule of activities (Appendix A and Appendix B) for the timing and frequency.
Change from baseline in haematology, clinical chemistry and urinalysis variables will be calculated for each post-dose visit on treatment. CTCAE (Version 5.0) grade will be calculated at each visit. Maximum post-baseline CTC will also be calculated. Absolute values will be compared to local laboratory reference ranges and classified as low (below range), normal (within range or on limits of range) and high (above range). All values classified as high or low will be flagged on the listings. During the study, clinically significant abnormal laboratory results not present at baseline should be reported as an AE.

Table 12 Laboratory safety variables

Haematology	**Clinical chemistry**
Haemoglobin	Albumin
Leukocyte	Alkaline phosphatase[b]
Absolute leukocyte differential count:	ALT[b]

• Neutrophils[a]	Amylase[c]
• Lymphocytes[a]	AST[b]
• Monocytes	Bicarbonate HCO_3[d]
• Basophils	Calcium, total
• Eosinophils	Chloride[d]
Platelet count	Creatinine clearance[d,e]
Coagulation	Gamma glutamyltransferase (GGT)[d]
Prothrombin Time	Glucose
Or	Lactate dehydrogenase (LDH)
International normalisation ratio (INR) and activated partial thromboblastin time (aPTT)	Lipase[c]
Urinalysis	Magnesium[d]
Bilirubin, blood, color and appearance, glucose, ketones, pH, protein, and specific gravity	Phosphate
	Potassium
	Sodium
	Total bilirubin[b]
Additional Tests	Total protein
Prostate specific antigen (PSA)	Urea nitrogen
CCI [redacted]	Uric acid
Testosterone[h]	Thyroid stimulating hormone (TSH)[f]
C-reactive protein (CRP)	Free T4[f]/Free T3[f]

a Can be recorded as absolute counts or as percentages. Absolute counts will be calculated by Data Management if entered as percentage. Total white cell count therefore has to be provided.
b Tests for ALT, AST, alkaline phosphatase, and total bilirubin must be conducted and assessed concurrently. If total bilirubin is ≥2 × upper limit of normal (and no evidence of Gilbert's syndrome), then fractionate into direct and indirect bilirubin.
c It is preferable that both amylase and lipase parameters are assessed. For sites where only 1 of these parameters is routinely measured, either lipase or amylase is acceptable.
d Bicarbonate (where available), chloride, creatinine clearance, gamma glutamyltransferase, magnesium, testing are to be performed at baseline, on Day 1 (unless all screening laboratory clinical chemistry assessments are performed within 3 days prior to Day 1), and if clinically indicated.
e Creatinine clearance will be calculated by using Cockcroft-Gault (using actual body weight).

f TSH is measured within 14 days prior to Day 1 (first infusion day), it does not need to be repeated at Day 1. Free T3 or free T4 will only be measured if TSH is abnormal or if there is a clinical suspicion of an AE related to the endocrine system.

3.6.7 Physical examination and weight

A physical examination will be performed and weight will be measured.
Physical examination will be performed at timelines as specified in the treatment arm schedule of activities (Appendix A and Appendix B). Investigators should pay special attention to clinical signs related to previous serious illnesses. New or worsening abnormalities may qualify as adverse events.

3.6.8 WHO Performance status

World Health Organisation (WHO) performance status will be assessed at the times specified in the schedule of assessments (Appendix AAppendix AAppendix AAppendix A and Appendix BAppendix B) based on the following:

Table 13 WHO Performance Status Scale

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

3.7 Pharmacokinetic variables

3.7.1 Pharmacokinetic samples

Serial venous blood samples for AZD4635 and cabazitaxel will be collected for analyses of AZD4635 and its metabolites (SSP-005173 and SSP-005174) and cabazitaxel plasma as outlined in the CSP.

Sparse PK samples for AZD4635 will be collected from Arm A participants. Up to approximately the first 12 evaluable Arm B participants will have additional PK sample for AZD4635 collected during Cycle 1 Day 1 and Day 2. Subsequent participants entering the study will have the sparse PK schedule. The same 12 evaluable Arm B participants will have cabazitaxel PK samples. Venous blood samples for analysis of durvalumab concentrations will be collected.

All post-dose PK samples will be collected at the specified time ± 5 min for the 0.5 hour time point, ± 10 min for the 1 and 1.5 hour time points and within ± 10% of the nominal time for later time points

(e.g. ± 12 min for a 2 hour sample) to be protocol compliant. The timing of the PK samples may be adjusted during the study, dependent on emerging data, in order to ensure appropriate characterisation of the plasma concentration-time profiles.

3.7.2 Pharmacokinetic parameters

Where data allow the following plasma pharmacokinetic (PK) parameters will be determined from the individual plasma concentration-time data of AZD4635, its metabolites (SSP-005173 and SSP-005174) and cabazitaxel. by non-compartmental analysis using the validated software program, Phoenix® WinNonlin® (Certara USA Inc., Version 8.1 or higher). Durvalumab PK parameters derivation is not planned due to sparse sample collection schedule. Durvalumab pre-dose and end of infusion concentrations will be summarized only.

Parameter	Definition
AUClast	Area under the plasma concentration-curve from zero to the last quantifiable concentration
AUC0-8	Partial area under the plasma concentration-time curve from time zero to 8 hours
AUC0-24	Partial area under the concentration-time curve from time zero to 24 hours
AUCinf	Area under plasma concentration-time curve from zero to infinity
Cmax	Maximum observed concentration
Tmax	Time of the maximum observed concentration
tlast	Time of the last quantifiable concentration
t½λz	Apparent terminal elimination half-life
CL/F	Apparent total body clearance of drug from plasma after extravascular administration (AZ4635 only)
CL	Total clearance (Cabazitaxel only)
Vz/F	Volume of distribution (apparent) at steady state following extravascular administration (based on terminal phase)(AZ4635 only)
Vz	Total volume of distribution during the terminal phase (Cabazitaxel only)
MRAUC	Metabolic ratio (based on AUCinf or AUClast as appropriate)
MRT	Mean residence time

Additional PK parameters may be calculated if appropriate. MRAUC may be corrected for molecular weight and free fraction as appropriate.

The molecular weight and free fraction values are as follows:

Molecular weight:

CCI [redacted]

Free fraction:

CCI [redacted]

The following diagnostic parameters for plasma PK analysis will be presented in the listings:

λz lower	Lower (earlier) t used for λz determination
λz upper	Upper (later) t used for λz determination
λzN	Number of data points used for λz determination
λz span	λz span ratio
Rsq	Statistical measure of fit for the regression used for λz determination
Rsq adj	Statistical measure of fit for the regression used for λz determination adjusted for the number of used data points (n obs)
AUCextr	Extrapolated area under the curve from tlast to infinity, expressed as percentage of AUCinf

4 ANALYSIS METHODS

4.1 General principles

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

- Descriptive statistics will be used for all variables, as appropriate. Continuous variables will be summarised by the number of observations, mean, standard deviation, median, minimum, and maximum. For log-transformed data, it is more appropriate to present geometric mean, geometric standard deviation, coefficient of variation (CV), median, minimum and maximum. Categorical variables will be summarised by frequency counts and percentages for each category.
  - Unless otherwise stated, percentages will be calculated out of the analysis set total (i.e. Arm A + Arm B) and for Arm B.
  - For continuous data, the mean and median will be rounded to 1 additional decimal place compared to the original data. The standard deviation will be rounded to 2 additional decimal places compared to the original data. Minimum and maximum will be displayed with the same accuracy as the original data.
- For categorical data, percentages will be rounded to 1 decimal place.
- Day to month conversion rule can be apply as Day=Month/12*365.25.
- For PK concentration data, all descriptive statistics will be presented to 4 significant figures, with the exception of minimum and maximum, which will be presented to 3 significant figures, and geometric CV% (to 1 significant figure). The listings will present the data to the same precision as received from the bioanalytical laboratory.
- For PK parameter data, the descriptive statistics will be presented according to the following conventions:
  - Cmax, AUClast, AUC0-8, AUC0-24, AUCinf, CL, CL/F, Vz/F, Vz, MRAUC, and MRT: descriptive statistics will be presented to 4 significant figures, with the exception of minimum and maximum, which will be presented to 3 significant figures.
  - tmax, tlast, t½λz: all descriptive statistics will be presented as received in the data, usually to 2 decimal places

- SAS® version 9.4 or higher will be used for all analyses.
- It is acceptable to present large numerical values in more appropriate units. For example, an AUC value of 123,000 ng·h/mL may be reported as 123 µg·h/mL instead of 123,000 ng·h/mL. It is, however, important to keep the units consistent within the report and the precision consistent with that prior to conversion.

There is more than one treatment in this study, thus the date of first dose is defined as the earliest date of dosing/administration of study treatment. The date of last dose is defined as the latest date of dosing/ administration of study treatment.

Assessments on the day of the first dose where neither time nor a nominal pre-dose indicator are captured will be considered prior to the first dose if such procedures are required by the protocol to be conducted before the first dose.

If relevant for the study, the following will be included due to the COVID-19 pandemic: participants affected by the COVID-19 pandemic will be listed including category for study disruption due to the pandemic and details of the disruption. If required, the study disruptions due to the pandemic will also be summarised. Subject disposition will be summarised including number (%) of participants who discontinued treatment due to the pandemic and who withdrew from study due to the pandemic. Important protocol deviations will be summarised including number (%) of participants with at least one important protocol deviation related to the pandemic.

4.2 Analysis methods

The two arms (Arm A and Arm B) will be analysed separately. Following the decision to stop enrolment in Arm A, data from Arm A will be listed only because the number of enrolled participants will be too small for a meaningful analysis. The analysis for Arm B will be descriptive, including summaries from the Kaplan-Meier curve.

4.2.1 Disposition, demography, and baseline characteristics

Disposition, demography, baseline characteristics (including disease characteristics), protocol deviations, disallowed concomitant medications, medical history and surgical history will be listed and summarised for safety analysis set for Arm B. Data from Arm A will be listed only.

4.2.1.1 Participant disposition

The reasons for each study treatment discontinuation and study discontinuation will be summarised with the number and percentage of participants. Percentages are calculated from number of participants who received treatment in Arm B. Data from Arm A will be listed only.

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

4.2.1.2 Analysis sets

The number and percentages of participants in each analysis set will be presented for Arm B.

- Safety
- DLT evaluable
- Pharmacokinetics (PK)

- FAS
- Tumour response evaluable
- Evaluable for Efficacy
- PSA Evaluable

The number and percentages of participants in interim tumour response evaluable analysis set and interim PSA evaluable analysis set will be presented for Arm B in the interim analysis.

4.2.1.3 Protocol deviations

The number and percentage of participants in the following categories will be summarised for Arm B:

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

Important protocol deviations will be listed for Arm A and Arm B. The examples of the categories are shown in Section 2.2.

4.2.1.4 Demography and baseline characteristics

The non-missing numerical values will be summarised as mean, median, standard deviation, minimum and maximum for Arm B; while the categorical values will be summarised as frequency and percentage for Arm B. Data from Arm A will be listed only.

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

4.2.1.5 Disease diagnosis and staging

The number and percentage of participants with the corresponding categorical values in disease diagnosis and staging will be summarised for Arm B including:

- WHO performance status
- Primary Tumour Location
- Histology Type
- Primary Tumour
- Regional Lymph Nodes
- Distant Metastases
- Tumour Grade
- Stage: American Joint Committee on Cancer (AJCC) stage at diagnosis, stage classification
- Total Gleason Score
- Time from diagnosis to enrolment

The extent of disease at entry of study will be summarised including:

- Evidence of disease (yes/no)
- Number of metastatic sites at study entry
- Metastatic/Locally Advanced

- Sites of Local/Metastatic Disease

PCWG3 Bone scan Baseline will be summarised including:
- Bone Scan Performed at baseline (yes/no)
- Number of Bone Scan Lesions at baseline
- Any Bone Lesion Out. Pelvis/Vertebra (yes, no)

4.2.1.6 Prior therapies

The number and percentage of participants in the following categories will be summarised for Arm B. Data from Arm A will be listed only.
- The number and percentage of participants with prior systemic therapy, prior radiographic therapy, and prior surgery at baseline.
- Summary of prior systemic therapy drugs by WHO preferred name
- Type of regimens of previous therapy at baseline

4.2.1.7 Concomitant medications

World Health Organization (WHO) Drug Dictionary version 23.0 will be used for coding medication terms.

Partial dates will be handled as follows to determine whether a medication is treatment emergent: For the start date: missing day only (assume Day 1 of each respective month), missing day and month (assume 1st January unless year is the same as first dose date then impute first dose date), completely missing (assume first dose date unless the end date suggests it could have started prior to this in which case impute the 1st January of the same year as the treatment start date). When imputing a start date ensure that the new imputed start date is sensible e.g. start date is before the end date. If the imputed start date is after the end date, keep the missing part of the start date as missing. For the end date: missing day only (assume last day of each respective month), missing day and month (assume 31st Dec), completely missing (assume 31st Dec of the same year as the treatment start date). When imputing an end date ensure that the new imputed date is sensible e.g. end date is after the start date. If the imputed end date is before the start date, keep the missing part of the end date as missing. Imputed dates are not to be used to calculate durations.

Concomitant medications will be summarized (frequency and percentage of patients) by ATC dictionary text and generic term for Arm B. Each unique drug will be counted once per participant. The summary will be ordered by decreasing total frequency of use in Arm B. Section 6.5.1 of the Clinical Study Protocol lists the prohibited medications for AZD4635, durvalumab and cabazitaxel, respectively. Disallowed concomitant medications will be summarized for Arm B. Disallowed concomitant medication will be listed together with all concomitant medication and will be flagged in the listing. Data from Arm A will be listed only.

4.2.1.8 Medical history

Medical history includes all conditions which begun prior to the study, regardless of whether or not they were ongoing during the study. Medical history will be coded using MedDRA version 23.0. The frequency and percentage of participants with each condition will be summarised by System Organ Class (SOC) and preferred term (PT) in Arm B. Participants with multiple unique terms will be counted once per each unique PT and unique SOC. Each summary will be ordered by decreasing frequency of PT within SOC.

4.2.2 Tumour response and efficacy

Tumour response data will be listed using the following response categories: CR, PR, SD, Non-CR/Non-PD, PD, and not evaluable (NE). Please note Non-CR/Non-PD will be only used for non-target lesions assessment.

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

4.2.2.1 Radiological progression-free survival (rPFS)

Summaries (number of events, medians, proportion and 95% confidence interval for progression free at fixed time points using the Kaplan-Meier estimate) and Kaplan-Meier plots will be provided for Arm B. A 2-sided 95% CI for the median rPFS will be produced in addition to the 25th and 75th percentiles.

4.2.2.2 Overall survival (OS)

Overall survival will be analysed in the same manner as rPFS if the number of participants with events allows.

4.2.2.3 Objective response rate (ORR) and Best objective response (BOR)

Best objective response and confirmed ORR will be summarised for Arm B. The BOR table will be presented for the evaluable for efficacy analysis set and separately for the tumour response evaluable analysis set. The tumour analysis set will be used for ORR. The proportion of participants achieving a confirmed objective response (CR or PR) will be presented with a two-sided 95% CI using the Clopper-Pearson method (Clopper C and Pearson E 1934).

The number and percentage of participants in each RECIST response category (CR, PR, SD, PD, Non-CR/Non-PD and NE) will be summarised for Arm B.

4.2.2.4 Change in tumour size

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

Waterfall plots indicating the best percentage change from baseline in sum of the diameters of target lesions will be produced for Arm B. The plot will present each participant's best percentage change from baseline in TL tumour size as a separate bar, with the bars ordered from the largest increase to the largest decrease. A reference line at the –30% change in TL tumour size level will be added to the plots, which corresponds with the definition of 'partial' response. Best overall response will be colour coded. The scale in these plots will be fixed to be from -100 to 100 to avoid presenting extreme values. Values that are capped as a result of this restriction to the scale are marked with '#'. Values will be ordered in descending order with the imputations due to death appearing first followed by a gap followed by all other participants.

Imputed values will be clearly marked with '*' and participants with imputation where there was a death or evidence of progression have different shading to each other and the other participants to make it clear that these are different.

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

4.2.2.5 Prostate-specific antigen (PSA) response

The proportion of participants achieving a PSA response and participants with a confirmed PSA response will be presented with 95% CI for Arm B. The best PSA percentage change from baseline will be summarised and graphed for Arm B. Waterfall plots (bar plots), and spider plots (individual line plots of percent change from baseline over time) will be produced for Arm B.

4.2.3 Patient reported outcomes

4.2.3.1 FACT-P

Summary statistics for FACT-P total score, FACT-P TOI, FAPSI-6, FAPSI-8, PCS and FWB as well as change in these scores from baseline will be presented for Arm B (including mean score, standard deviation, median and range) for all visits until there are less than 10 participants with evaluable data in Arm B to present in the outputs. Data from Arm A will only be listed.

The proportion of participant with best responses of 'Improved', 'No Change' and "Worsened" will be presented with a two-sided 95% CI using the Clopper-Pearson Method (Clopper C and Pearson E 1934) for FACT-P total score, FACT-P TOI, FAPSI-6, PCS and FWB.

Time to deterioration of FACT-P total score will be assessed using the same methods as for the primary analysis. In addition, the time to deterioration for the subscales of the FACT-P (FACT-P TOI, FAPSI-6, PCS and FWB) will be presented as well.

4.2.3.2 BPI-SF

Summary statistics for worst pain (BPI-SP item 3), average pain (BPI-SP item 5), pain severity (Questions 3, 4, 5 and 6) and pain inference (Question 9 A-G) in BPI-SP as well as change in these scores from baseline will be presented for Arm B (including mean score, standard deviation, median and range) for all visits until there are less than 10 participants with evaluable data in Arm B to present in the outputs. Data from Arm A will only be listed.

Proportion of participants with improved, stable, or deteriorated pain score compared to baseline at each time point will be summaries for Arm B.

Time to pain progression in BPI-SF, the summary (number of events, medians and 95% confidence interval for pain progression free at fixed time points using the Kaplan-Meier estimate) will be provided for Arm B. A 2-sided 95% CI for the median of time to pain progression will be produced in addition to the 25th and 75th percentiles.

Participants who have not experienced pain progression at the time of analysis will be censored on the last known date when a participant was known to have not progressed. Participants with no on-study assessment or no baseline assessment will be censored at Day 1.

4.2.4 Safety analyses

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

4.2.4.1 Exposure

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

Reasons for discontinuation of investigational product will be listed including the study day of treatment discontinuation for both arms and will be summarized for Arm B if appropriate.

Total exposure, number of infusion cycles (where applicable), total treatment duration (as defined in Section 3.6.1), and the amount delivered relative to the intended amount (dose intensity: RDI) will be summarised by the following: number of observations, mean, standard deviation, median, minimum, Q1, Q3 and maximum. The number and percentage of participants with at least one dose interruption and dose reductions for AZD4635, the number and percentage of participants with at least one delay and at least one dose interruption for Durvalumab, the number and percentage of participants with at least one delay, at least one dose reduction and at least one dose interruption for Cabazitaxel will be presented.

A swimmer plot will be produced for duration of exposure of study treatment for Arm B.

4.2.4.2 Adverse Events/Serious adverse events

Adverse events will be listed individually by participant and treatment arm. The number of participants experiencing each AE will be summarised by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class, MedDRA preferred term, and CTCAE grade. Participants with multiple events in the same category are counted only once in that category. Participants with events in more than 1 category are counted once in each of those categories. Each participant is represented with the maximum reported intensity only for each preferred term. Each participant is represented by the maximum reported relationship for each preferred term. Number and percentage of participants with adverse events possibly related to any study treatment will summarised by system organ class, preferred term and maximum reported CTCAE grade for Arm B.

Number and percentage of participants with adverse events, most common (frequency of >10%) will be summarised by preferred term in Arm B; Number and percentage of participants with adverse events possibly related to any study treatment, most common (frequency of >10%) will be summarised by preferred term for Arm B.

The number and percentage of participants with AEs in different categories (e.g., possibly related, CTCAE Grade ≥ 3, etc.) will be summarised by Arm B, and events in each category will be further summarised by MedDRA system organ class and preferred term, by Arm B. Serious AEs will be summarised separately if a sufficient number occur.

Any AE occurring before the first dose of IP (i.e., before study Day 1) will be included in the data listings, but will not be included in the summary tables of AEs.

Any AE occurring within the defined follow-up period after discontinuation of IP will be included in the AE summaries. Any AEs in this period that occur after a participant has received further therapy for cancer (following discontinuation of IP) will be flagged in the data listings. Adverse events

occurring after the 30-day or 90-day follow-up period after discontinuation of IP will be listed, but not included in the summaries.
Generally, the imputation of dates is used to decide if an observation is treatment emergent for adverse events or concomitant medications. The imputed dates are not advised to be used to calculate durations where the results would be less accurate. After querying, dates will be imputed as follows:

- For missing AE start dates, the following will be applied:
  - Missing day - Impute the 1st of the month unless month is the same as month of the first dose of study drug then impute first dose date.
  - Missing day and month - Impute 1st January unless year is the same as first dose date then impute first dose date.
  - Completely missing - Impute first dose date unless the end date suggests it could have started prior to this in which case impute the 1st January of the same year as the end date.
  - When imputing a start date ensure that the new imputed start date is sensible e.g. start date is before the end date. If the imputed start date is after the end date, keep the missing part of the start date as missing.
- For missing AE end dates, the following will be applied:
  - Missing day - Impute the last day of the month.
  - Missing day and month – Impute 31st December.
  - When imputing an end date ensure that the new imputed date is sensible e.g. end date is after the start date. If the imputed end date is before the start date, keep the missing part of the end date as missing.

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

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

Separate tables will present adverse events leading to discontinuation, serious adverse events and other significant adverse events. All AE data will be listed appropriately.
Cause of death will be summarised and the details of any deaths will be listed for all participants.
In addition, adverse events of special interest will be summarised. The listing of preferred terms and categories will be provided by the medical team at end of study prior to database lock (DBL). All AESI will be flagged in the AE listing.
Summaries of the above-mentioned grouped AE categories will include number (%) of participants who have:

- At least one AESI for Durvalumab, by CTCAE grade
- At least one possibly related AESI for Durvalumab, by CTCAE grade

Dose-limiting toxicity (DLT) which is defined in Protocol section 6.6.1 will be recorded in eCRF when it occurs to the first 6 evaluable participants. Number of evaluable participants with a DLT will be summarised for Arm B for DLT analysis set. The participant ID, AE preferred term and CTCAE grade will be listed.

4.2.4.3 Electrocardiographic (ECG)

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

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

4.2.4.4 Vital signs assessment (VS) including Height and Weight

Vital signs (resting heart rate, systolic and diastolic blood pressure, respiration rate, and body temperature), and height (at screening only) will be summarised for the safety analysis set.

- Result and percentage change from baseline by visit for Arm B (including mean, median, standard deviation, maximum, and minimum)

4.2.4.5 Laboratory data

Change from baseline in haematology, clinical chemistry, urinalysis and coagulation variables will be calculated for each post-dose visit on treatment. CTCAE (version 5.0) grade will be calculated at each visit for Arm B. Maximum post-baseline CTC will also be calculated for Arm B. Absolute values will be compared to local laboratory reference ranges and classified as low (below range), normal (within range or on limits of range) and high (above range). All values classified as high or low will be flagged on the listings. Participants with potential Hy's Law will be listed, it includes all participants who have ALT or AST≥3 time of upper limit of normal (ULN) together with total bilirubin (TBL) ≥2 time of ULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP). In this table the value of individual ALT, AST and total bilirubin at each visit together with the upper limit of normal will be displayed.

4.2.4.6 Physical Examination

New or aggravated findings, as compared with baseline, on the physical examinations are to be reported as AEs.

4.2.5 Pharmacokinetics data

The plasma concentrations will be listed and presented in tabular and graphical form as appropriate according to AZ standards. The PK parameters will be listed and summarized. All PK tables, figures and listings will be performed only at Final Analysis. Any individual PK data excluded from the PK Analysis Set or the PK summaries will be flagged with an appropriate footnote in the listings by the PK Scientist.

4.2.5.1 Plasma concentration data

Summaries of reportable PK concentrations and parameters will be presented for the PK Analysis Set for Arm B, unless otherwise specified. Data from Arm A will only be listed. For each analyte, plasma concentrations for each scheduled time-point will be summarized by PK Day/Visit and Treatment using appropriate descriptive statistics. Where possible, the following descriptive statistics will be presented:

- The geometric mean (gmean, calculated as exp [μ], where μ is the mean of the data on a logarithmic scale)
- The geometric standard deviation (geoSD, calculated as exp[s], where s is the standard deviation of the data on a loge scale)

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

A listing of all concentration-time data will be presented by visit for each arm, PK Day/Visit and Treatment. Listings of individual PK blood sample collection times (against derived sampling time deviations), concentrations and parameters will be presented for the Safety Analysis Set. Individual concentrations with time deviations of greater than ±10% from the protocol scheduled time, will be used in the PK analysis but will be flagged for exclusion from the summary tables and corresponding figures. Data from participants excluded from the pharmacokinetic population will be included in the data listings, but not in the summaries. Data from participants excluded from the pharmacokinetic population will be provided by Covance PK expert.

Handling of PK results below lower limit of quantification

Individual compound concentrations below the LLoQ of the assay are reported as NQ (not quantifiable) with the LLoQ mentioned in respective tables, figures and listings.
For descriptive statistics:

- If, at a given time point, 50% or less of the plasma concentrations are NQ, the geometric mean, geometric CV%, arithmetic mean and SD will be calculated by substituting the LLoQ for values which are NQ.
- If more than 50%, but not all, of the concentrations are NQ, the geometric mean, geometric CV%, arithmetic mean and SD will be reported as not calculable (NC). The maximum value will be reported from the individual data, and the minimum and median will be set as NQ.
- If all the concentrations are NQ, the geometric mean and arithmetic mean are reported as NQ and the geometric CV% and arithmetic SD as NC.
- The number of values below LLoQ will be reported for each time point along with the total number of collected values.

Three observations >LLoQ will be required as a minimum for a plasma concentration or PK parameter to be summarised. Two values will be presented as a minimum and maximum with the other summary statistics as NC.

For consistency, the same plasma concentration values will be used in the mean data graphs as those given in the descriptive statistics summary table for each time point.

According to the PK Sampling Schedule (Protocol section 8.5.1), figures in this study will be provided for AZD4635 and cabazitaxel for the first 12 evaluable participants in Arm B. All figures will be based on the PK analysis set for Arm B. Figures for the geometric mean concentration-time

data will be presented, in both a linear and semi-logarithmic scale (SD only on the linear scale). The descriptive statistics presented in the summary concentration table will be used to create these plots.

4.2.5.2 Pharmacokinetic Parameters

Calculation or derivation of PK parameters

The PK analyses of the plasma concentration data for AZD4635 and its metabolites (SSP-005173 and SSP-005174) and cabazitaxel will be performed by Covance, on behalf of the Clinical Pharmacokinetic Alliance, AstraZeneca R&D. Durvalumab pre-dose and end of infusion concentrations will be summarized only. PK parameters will be derived using non-compartmental methods in Phoenix® WinNonlin® Version 8.1 or higher (Certara). PK analysis will, where data allow, be carried out using the actual elapsed times relative to time of dosing. If actual elapsed times are missing, nominal times may be used at the discretion of the PK Scientist with approval from the AZ Clinical Pharmacology Scientist (CPS).

Concentration data will be used as supplied by the analytical laboratory for PK analysis. The units of concentration and resulting PK parameters will be presented as they are received from the analytical laboratory unless otherwise specified in the PK order form.

If an entire concentration-time profile is not quantifiable, the profile will be excluded from the PK analysis.

Cmax, Cmin, tmax, and tlast, will be taken directly from the concentration-time profiles. In the case where multiple peaks are of equal magnitude are present, the earliest tmax will be reported.

Where there are sufficient data, λz will be calculated for the derivation of regression based parameters (e.g. t½□z, AUCinf, CL, CL/F, Vz, Vz/F). Where t½λz is estimated over the period of less than three half-lives, the value may be flagged in the data listings. An Rsq adj value of ≥0.8 indicate good fit of the log-linear regression. Any □z with a Rsq_adj of <0.8 may be flagged in the data listings along with the regression based parameters.

The minimum requirement for the calculation of AUCs will be the inclusion of at least 3 consecutive quantifiable concentrations. Where there are only 3 quantifiable concentrations at least one of these should follow the peak concentration.

PK parameter listings

All reportable PK parameters, including individual diagnostic and lambda z related parameters, will be listed for each participant by PK Day/Visit and Treatment, for each analyte separately.

PK parameter descriptive statistics

All primary and secondary PK parameters will be summarized for each analyte by PK Day/Visit for the first 12 evaluable participants in Arm B using appropriate descriptive statistics. Where possible, the following descriptive statistics will be presented for PK parameters except for tmax and tlast.

- Gmean, calculated as exp[μ], where μ is the mean of the data on a logarithmic scale
- geoSD, calculated as exp[s], where s is the standard deviation of the data on a $\log_e$ scale
- CV, calculated as 100 $\sqrt{}$ [exp(s^2)-1], where s is the standard deviation of the data on a $\log_e$ scale
- Gmean + geoSD (calculated as exp[μ+s])

- Gmean - geoSD (calculated as exp[μ-s])
- Arithmetic mean calculated using untransformed data
- Standard deviation calculated using untransformed data
- Median
- Minimum
- Maximum
- Number of observations

The following summary statistics will be presented for the diagnostic PK parameters λz lower, λz upper, λzN, Rsq, Rsq adj, AUCextr and λz span:

- Arithmetic mean
- Standard deviation
- Median
- Minimum
- Maximum
- Number of observations

The following summary statistics will be presented for tmax and tlast:

- Median
- Minimum
- Maximum
- Number of observations

By-participant listings of PK parameters for the first 12 evaluable participants in Arm B will be provided. Data from participants excluded from the PK analysis set will be included in the data listings but not in the descriptive statistics.

4.2.6 Other analysis

CCI [redacted] The secondary PK analyses will be reported in the main CSR.

5 SAFETY REVIEW COMMITTEE

Once the first 6 evaluable participants complete at least 1 cycle of study treatment on Arm B, the safety and tolerability of the combination of AZD4635 plus durvalumab plus cabazitaxel will be assessed by the SRC. The SRC will evaluate all available toxicity information (including AEs and laboratory abnormalities that are not DLTs (defined in Protocol Section 6.6.1), as well as available PK and PD information. In the case of safety and tolerability concerns at any point during this time, the study team will consider halting recruitment until full analysis and review by the SRC is performed but otherwise recruitment will continue through the period of review by the SRC.

The SRC will consist of:

- AstraZeneca Study Team Physician, who will chair the committee, or delegate
- Parexel Study Team Physician or delegate
- Principal Investigator or delegate from the enrolled participants' investigational site
- Global Safety Physician or delegate

Other Principal Investigators and representatives from AstraZeneca and Parexel, such as Study Pharmacokineticist, Study Statistician, Patient Safety Scientist, Study Delivery Leader may also be invited as appropriate. The SRC Remit document for this study will define the exact membership and who should be present for decisions to be made.

Further internal or external experts may be consulted by the SRC as necessary. The Global Safety Physician or delegate should always be present at the SRC if there are safety issues for discussion.
The decision may be to:

- Proceed with recruitment to Arm B
- Enrol a further 3 to 6 evaluable participants and/or
- Modify or reduce the dose either by adjustment of dose levels or schedule. (For instance, if there are any concerns about tolerability the dose of AZD4635 may be reduced to [redacted] mg PO daily from [redacted] mg daily.)
- Stop further recruitment to Arm B

The SRC decision will be shared with all Investigators. Date extracted from EDC will be provided to SRC for reviewing.

6 INTERIM ANALYSIS

Given the limited data available with the triplet combination, a futility interim analysis is planned for Arm B based on PSA50 response and will be triggered according to the following: after approximately n = 30 dosed participants for the arm have had the opportunity for sample collection for PSA response at the start of Week 13. It will be based on a decision framework (Frewer et al. 2016) using predictive probability of a good signal being observed at the final analysis. Based on a decision framework (Frewer et al. 2016) with a TV of 55% and a LRV of 35%, a greater than 80% probability of PSA50 response >35% may be considered a good signal. Using predictive probability of a good signal being observed at the final analysis and fixing the acceptable risk of an incorrect decision to stop to be a maximum of 10%, leads to a futility stop decision if only 11/30 or fewer (≤ 37%) PSA responses are observed at the time of the interim for example. When the true PSA50 response rate is 20%, the probability of stopping at the interim is 99%. When the true PSA50 response rate is 35%, the probability of a stop rule being met at both the interim and primary analysis is 65%; the probability of incorrectly stopping at the interim is 0% and incorrectly going at the interim is 3%. When the true PSA50 response rate is 55%, the probability of incorrectly stopping at the interim is only 2%. Other data available at the time will also be considered. Other data available at the time will also be considered. This is planned for the assessment of futility, such that further recruitment into the arm may be stopped. However, participants already recruited would continue to be followed. Participant recruitment will be paused during the time of the interim analysis once the number of dosed participants in Arm B reaches approximately 35 to ensure 30 evaluable participants for the PSA50 response. Of these participants, approximately 15 participants are to have RECIST v1.1 measurable disease at baseline and the remainder of the participants may have bone-only disease or measurable disease.
The following outputs will be produced for interim if required.

Demographics

- Disposition
- Analysis sets
- Demographic characteristics
- Participant characteristics
- Prior therapies at baseline (including type of regimens)

- Disease characteristics at baseline

Efficacy

- Radiographic progression-free survival
- Best objective response
- Best percentage change from baseline
- Duration of objective response
- TL percentage change from baseline
- PSA response
- PSA best percentage change from baseline

Exposure, and Safety

- Duration of exposure
- Selected AE outputs and deaths

Section 3.2 list of outputs in TFL shells provide more details.

Interim tumour response evaluable analysis set and interim PSA evaluable analysis set are defined in Section 2.1. Best objective response will be produced for interim tumour response evaluable analysis set (and for tumour response evaluable set and evaluable for efficacy set as supportive) and PSA response will be produced for interim PSA evaluable analysis set (and PSA evaluable set as supportive). 80% CI instead of 95% CI of best objective response rate and PSA50 response rate will be presented for the interim analysis. Unconfirmed response will be displayed together with confirmed response in duration of response swimmer plot for the interim analysis.

7 CHANGES OF ANALYSIS FROM PROTOCOL

The SAP has been updated based on Protocol Amendment 2, 24-November-2020.

Interim tumour response evaluable analysis set and interim PSA evaluable analysis set have been added to section 2.1 and details of outputs for these additional analysis sets have been included in the Interim Analysis section 6. The outputs to be produced for the interim analysis have also been added.

CCI [redacted]

8 REFFERENCES

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9 APPENDIX

Appendix A Schedule of Activities for Arm A (AZD4635 plus Durvalumab every 4 Weeks)

	Screening	Cycle = 28 days (4 weeks)								End-of-Treatment	Follow-up Visits				Details in CSP Section or Appendix
		Cycle 1			Cycle 2		Cycle 3		Cycle 4 onwards		30-days (±7 days) after last treatment	90-days (±7 days) after last treatment	Progression-Free Follow-Up[a] (Every 12 weeks [±7 days])	Survival 90 days (Every 3 months (±7 days) after last treatment, until final DCO)	
Week	**-4 to -0**	**1**	**2**	**3**	**5**	**7**	**9**	**11**	**13+**						
Day (visit window ±3 days from Cycle 2, Day 1 onwards)	**-28 to 0**	**1**	**8**	**15**	**1**	**15**	**1**	**15**	**1**						
Informed consent	X														5.1
Inclusion/exclusion criteria	X														5.1, 5.2
Routine clinical procedures[b]															
Medical history and demographics	X														5.1, 5.2
Physical examination including weight	X	X			X		X		X	X					8.2.1
WHO performance status	X	X			X		X		X						8.2.2, Table 14
Test for COVID-19[c]	Tests for active COVID-19 infection may be prescribed, if required.														8.2.8
Vital signs including respirations	X	X			X		X		X	X					8.2.3
Height	X	X													8.2.3
12-lead ECG (triplicate)	X (≤14 days)	X								X					8.2.4
Echocardiogram/MUGA	X[d]														8.2.5

Appendix A Schedule of Activities for Arm A (AZD4635 plus Durvalumab every 4 Weeks)

	Screening	Cycle = 28 days (4 weeks)								End-of-Treatment	Follow-up Visits				Details in CSP Section or Appendix
		Cycle 1			Cycle 2		Cycle 3		Cycle 4 onwards		30-days (±7 days) after last treatment	90-days (±7 days) after last treatment	Progression-Free Follow-Up[a] (Every 12 weeks [±7 days])	Survival 90 days (Every 3 months (±7 days) after last treatment, until final DCO)	
Week	**-4 to -0**	**1**	**2**	**3**	**5**	**7**	**9**	**11**	**13+**						
Day (visit window ±3 days from Cycle 2, Day 1 onwards)	**-28 to 0**	**1**	**8**	**15**	**1**	**15**	**1**	**15**	**1**						
Concomitant (including prior) medication	X	At every visit and may be conducted by phone if not tied to a visit.								X	X	X (Cancer therapy only at these 2 visits)			8.2.6

Appendix A Schedule of Activities for Arm A (AZD4635 plus Durvalumab every 4 Weeks)

	Screening	Cycle = 28 days (4 weeks)								End-of-Treatment	Follow-up Visits				Details in CSP Section or Appendix
		Cycle 1			Cycle 2		Cycle 3		Cycle 4 onwards		30-days (±7 days) after last treatment	90-days (±7 days) after last treatment	Progression-Free Follow-Up[a] (Every 12 weeks [±7 days])	Survival 90 days (Every 3 months (±7 days) after last treatment, until final DCO)	
Week	**-4 to -0**	**1**	**2**	**3**	**5**	**7**	**9**	**11**	**13+**						
Day (visit window ±3 days from Cycle 2, Day 1 onwards)	**-28 to 0**	**1**	**8**	**15**	**1**	**15**	**1**	**15**	**1**						
Routine safety measurements[b]															
Adverse events	X	At every visit and may be conducted by phone if not tied to a visit.								X	X	X	X		Appendix B
Haematology	X	X		X	X	X	X		X	X					8.2.7, Table 15
Clinical chemistry	X	X		X	X	X	X		X	X					8.2.7, Table 15
Urinalysis	X	X			X		X		X						8.2.7, Table 15
Coagulation (PT/INR/aPTT)	X				X		X		X	X					8.2.7, Table 15
Testosterone level	X														8.2.8
Pharmacokinetic measurements															
AZD4635 pre-dose blood sample		X					X		X (C5 & C7 only)						8.5.1, Table 16
Durvalumab pre-infusion blood sample for PK		X			X				X (C4 & C7 only)						8.5.2, Table 20
Durvalumab post-infusion blood sample for PK		X							X (C4 only)			X			8.5.2, Table 20

Appendix A Schedule of Activities for Arm A (AZD4635 plus Durvalumab every 4 Weeks)

	Screening	Cycle = 28 days (4 weeks)								End-of-Treatment	Follow-up Visits				Details in CSP Section or Appendix
		Cycle 1			Cycle 2		Cycle 3		Cycle 4 onwards		30-days (±7 days) after last treatment	90-days (±7 days) after last treatment	Progression-Free Follow-Up[a] (Every 12 weeks [±7 days])	Survival 90 days (Every 3 months (±7 days) after last treatment, until final DCO)	
Week	-4 to -0	1	2	3	5	7	9	11	13+						
Day (visit window ±3 days from Cycle 2, Day 1 onwards)	-28 to 0	1	8	15	1	15	1	15	1						
Durvalumab pre-infusion blood sample for anti-drug antibody		X			X				X (C4 & C7 only)			X			8.5.2, Table 20
Biomarker assessments															
CCI															

Appendix A Schedule of Activities for Arm A (AZD4635 plus Durvalumab every 4 Weeks)

	Screening	Cycle = 28 days (4 weeks)								End-of-Treatment	Follow-up Visits				Details in CSP Section or Appendix
		Cycle 1			Cycle 2		Cycle 3		Cycle 4 onwards		30-days (±7 days) after last treatment	90-days (±7 days) after last treatment	Progression-Free Follow-Up[a] (Every 12 weeks [±7 days])	Survival 90 days (Every 3 months (±7 days) after last treatment, until final DCO)	
Week	**-4 to -0**	**1**	**2**	**3**	**5**	**7**	**9**	**11**	**13+**						
Day (visit window ±3 days from Cycle 2, Day 1 onwards)	**-28 to 0**	**1**	**8**	**15**	**1**	**15**	**1**	**15**	**1**						
Pharmacogenetic sampling (optional)															
CCI [redacted]		[redacted]													[redacted]
Efficacy measurements															
Tumour imaging (RECIST Version 1.1) CT/MRI/PET[f]	X	**Every 8 wks (±1 wk) from the start of dosing until 24 wks, and then every 12 wks (±1 wk) thereafter**								X (if required)			X		8.1.1
Tumour imaging (PCWG3 for bone lesion assessment) Bone scans	X	**Every 8 wks (±1 wk) from the start of dosing until 24 wks, and then every 12 wks (±1 wk) thereafter**								X (if required)			X		8.1.2
PSA	X	X			X		X		X	X			X		8.2.8
CCI [redacted]	[redacted]	[redacted]			[redacted]		[redacted]		[redacted]	[redacted]			[redacted]		[redacted]
Survival status/subsequent cancer therapy														X	8.2.10.3
ePRO (BPI-SF)[g]		X			X		X		X	X	X		X		8.2.9
ePRO (FACT-P)[g]		X			X		X		X	X	X		X		8.2.9
Study intervention administration															

Appendix A Schedule of Activities for Arm A (AZD4635 plus Durvalumab every 4 Weeks)

	Screening	Cycle = 28 days (4 weeks)								End-of-Treatment	Follow-up Visits				Details in CSP Section or Appendix
		Cycle 1			Cycle 2		Cycle 3		Cycle 4 onwards		30-days (±7 days) after last treatment	90-days (±7 days) after last treatment	Progression-Free Follow-Up[a] (Every 12 weeks [±7 days])	Survival 90 days (Every 3 months (±7 days) after last treatment, until final DCO)	
Week	**-4 to -0**	**1**	**2**	**3**	**5**	**7**	**9**	**11**	**13+**						
Day (visit window ±3 days from Cycle 2, Day 1 onwards)	**-28 to 0**	**1**	**8**	**15**	**1**	**15**	**1**	**15**	**1**						
AZD4635 dispensed (daily dosing)		→													6.2.1
Diary review		X			X		X		X						6.2.1, 6.4
Durvalumab 1500 mg IV		X			X		X		X						6.2.2.1

a Participants will be followed up every 12 weeks (±1 week) starting from the last date of the last tumour response assessment until either: objective PD has been confirmed, withdrawal of consent, until the primary DCO for the arm, or until the study is terminated by the Sponsor.

b Routine clinical and safety assessments may be done 1 day prior to each visit, if required.

c During the study, tests for active COVID-19 infection may be prescribed, if required, and in accordance with local guidelines.

d An echocardiogram or multiple-gated acquisition (MUGA) scan obtained in the 6 months prior to screening will be acceptable unless there has been a change in the participant's cardiac status, in which case this will be repeated. If there is no echocardiogram or MUGA within 6 months prior to study enrollment, this will be performed at screening. Additional assessments for echocardiogram or MUGA during the study will be determined as clinically indicated based on the current available data.

CCI [redacted]

f Per Protocol Appendix G, while PET scans are not considered adequate to measure lesions, PET-CT scans may be used providing that the measures are obtained from the CT scan and the CT scan is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast).

g The PRO instruments will be administered and completed at the start of each visit.

Appendix B Schedule of Activities for Arm B (AZD4635 plus Durvalumab and Cabazitaxel every 3 Weeks for First 10 Cycles and then every 4 Weeks)

	Screening	Cycle = 21 days (3 weeks)										Cycle = 28 days (4 weeks)	End-of-Treatment	Follow-up Visits				Details in CSP Section or Appendix
		Cycle 1				Cycle 2			Cycle 3		Cycle 4 to 10	Cycle 11 onwards						
Week	**-4 to -0**	**1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**9**	**10-32**	**33+**		**30-days (±7 days) after last treatment**	**90-days (±7 days) after last treatment**	**Progression-free survival[a] (Every 12 weeks [±7 days])**	**Survival 90 days (Every 3 months (±7 days) after last treatment, until final DCO)**	
Day (visit window ±3 days from Cycle 2, Day 1 onwards)	**-28 to 0**	**1**	**2**	**8**	**15**	**1**	**8**	**15**	**1**	**15**	**1**	**1**						
Informed consent	X																	5.1
Inclusion/exclusion criteria	X																	5.1, 5.2
Routine clinical procedures[b]																		
Medical history and demographics	X																	5.1, 5.2
Physical examination including weight	X	X				X			X		X	X	X					8.2.1
WHO performance status	X	X				X			X		X	X						8.2.2, Table 14
Test for COVID-19[c]	Tests for active COVID-19 infection may be prescribed, if required.																	8.2.8
Vital signs including respirations	X	X				X			X		X	X	X					8.2.3
Height	X	X																8.2.3
12-lead ECG (triplicate)	X (≤14 days)	X											X					8.2.4
Echocardiogram/ MUGA	X[d]																	8.2.5

Appendix B Schedule of Activities for Arm B (AZD4635 plus Durvalumab and Cabazitaxel every 3 Weeks for First 10 Cycles and then every 4 Weeks)

	Screening	Cycle = 21 days (3 weeks)									Cycle = 28 days (4 weeks)	End-of-Treatment	Follow-up Visits				Details in CSP Section or Appendix
		Cycle 1				Cycle 2			Cycle 3		Cycle 4 to 10	Cycle 11 onwards					
Week	**-4 to -0**	**1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**9**	**10-32**	**33+**		**30-days (±7 days) after last treatment**	**90-days (±7 days) after last treatment**	**Progression-free survival[a] (Every 12 weeks [±7 days])**	**Survival 90 days (Every 3 months (±7 days) after last treatment, until final DCO)**	
Day (visit window ±3 days from Cycle 2, Day 1 onwards)	**-28 to 0**	**1**	**2**	**8**	**15**	**1**	**8**	**15**	**1**	**15**	**1**	**1**						
Concomitant (including prior) medication	X	At every visit and may be conducted by phone if not tied to a visit.									X	X	X	X	X (Cancer therapy only at these 2 visits)			8.2.6
Routine safety measurements[a]																		
Adverse events	X	At every visit and may be conducted by phone if not tied to a visit.									X	X	X	X	X	X		Appendix B
Haematology[e]	X	X	X	X	X	X	X	X	X		X	X	X					8.2.7, Table 15
Clinical chemistry	X	X	X	X	X	X	X	X	X		X	X	X					8.2.7, Table 15
Urinalysis	X	X				X			X		X	X						8.2.7, Table 15
Coagulation (PT/INR/aPTT)	X					X			X		X	X	X					8.2.7, Table 15
Testosterone level	X																	8.2.8, Table 15

Appendix B Schedule of Activities for Arm B (AZD4635 plus Durvalumab and Cabazitaxel every 3 Weeks for First 10 Cycles and then every 4 Weeks)

	Screening	Cycle = 21 days (3 weeks)										Cycle = 28 days (4 weeks)	End-of-Treatment	Follow-up Visits				Details in CSP Section or Appendix
		Cycle 1				Cycle 2			Cycle 3		Cycle 4 to 10	Cycle 11 onwards						
Week	**-4 to -0**	**1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**9**	**10-32**	**33+**						
Day (visit window ±3 days from Cycle 2, Day 1 onwards)	**-28 to 0**	**1**	**2**	**8**	**15**	**1**	**8**	**15**	**1**	**15**	**1**	**1**		**30-days (±7 days) after last treatment**	**90-days (±7 days) after last treatment**	**Progression-free survival[a] (Every 12 weeks [±7 days])**	**Survival 90 days (Every 3 months (±7 days) after last treatment, until final DCO)**	
Pharmacokinetic measurements																		
First 12 evaluable participants																		
Pre-dose AZD4635, durvalumab and cabazitaxel blood sample		X				X (AZD4635 only)			X (AZD4635 only)		X (C5 & C7) (AZD4635 only)							8.5.1, Table 17
AZD4635 post-dose blood samples		X	X															8.5.1, Table 17
Cabazitaxel post-dose blood samples		X	X															Table 19
All participants (excluding first 12 evaluable participants)																		
AZD4635 pre-dose blood sample		X							X		X (C5 & C7)							8.5.1, Table 18
Durvalumab pre-infusion blood sample for PK		X				X					X (C4 & C7)							8.5.2, Table 20
Durvalumab post-infusion blood sample for PK		X									X (C4 only)				X			8.5.2, Table 20

Appendix B Schedule of Activities for Arm B (AZD4635 plus Durvalumab and Cabazitaxel every 3 Weeks for First 10 Cycles and then every 4 Weeks)

	Screening	Cycle = 21 days (3 weeks)										Cycle = 28 days (4 weeks)	End-of-Treatment	Follow-up Visits				Details in CSP Section or Appendix
		Cycle 1				Cycle 2			Cycle 3		Cycle 4 to 10	Cycle 11 onwards						
Week	-4 to -0	1	1	2	3	4	5	6	7	9	10-32	33+		30-days (±7 days) after last treatment	90-days (±7 days) after last treatment	Progression-free survival[a] (Every 12 weeks [±7 days])	Survival 90 days (Every 3 months (±7 days) after last treatment, until final DCO)	
Day (visit window ±3 days from Cycle 2, Day 1 onwards)	-28 to 0	1	2	8	15	1	8	15	1	15	1	1						
Durvalumab pre-infusion blood sample for anti-drug antibody		X				X					X (C4 & C7 only)				X			8.5.2, Table 20
Biomarker																		
CCI [redacted]		■	■															■
[redacted]		■	■			■			■		■	■	■					■
[redacted]			■		■	■			■		■	■		■				■
[redacted]		■	■				■		■	■	■							■
CCI [redacted]		■																■

Appendix B Schedule of Activities for Arm B (AZD4635 plus Durvalumab and Cabazitaxel every 3 Weeks for First 10 Cycles and then every 4 Weeks)

	Screening	Cycle = 21 days (3 weeks)										Cycle = 28 days (4 weeks)	End-of-Treatment	Follow-up Visits				Details in CSP Section or Appendix
		Cycle 1				Cycle 2			Cycle 3		Cycle 4 to 10	Cycle 11 onwards						
Week	**-4 to -0**	**1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**9**	**10-32**	**33+**		**30-days (±7 days) after last treatment**	**90-days (±7 days) after last treatment**	**Progression-free survival[a] (Every 12 weeks [±7 days])**	**Survival 90 days (Every 3 months (±7 days) after last treatment, until final DCO)**	
Day (visit window ±3 days from Cycle 2, Day 1 onwards)	**-28 to 0**	**1**	**2**	**8**	**15**	**1**	**8**	**15**	**1**	**15**	**1**	**1**						
Paired tumour biopsies (optional)	X	X			X (Day 14-19)								X (at PD for responders)					8.6.2.1
Pharmacogenetic sampling (optional)																		
CCI [redacted]		[redacted]																[redacted]
Efficacy measurements																		
Tumour imaging (RECIST Version 1.1) CT/MRI/PET[f]	X[g]					**Every 9 wks (±1 wk) from the start of dosing until 27 wks, and then every 12 wks (±1 wk) thereafter**							X (if required			X			8.1.1
Tumour imaging (PCWG3 for bone lesion assessment) Bone scans	X					**Every 9 wks (±1 wk) from the start of dosing until 27 wks, and then every 12 wks (±1 wk) thereafter**							X (if required			X			8.1.2
PSA	X	X				X			X		X	X	X			X		8.2.8
CCI [redacted]	[redacted]	[redacted]				[redacted]			[redacted]		[redacted]	[redacted]	[redacted]			[redacted]		[redacted]

Appendix B Schedule of Activities for Arm B (AZD4635 plus Durvalumab and Cabazitaxel every 3 Weeks for First 10 Cycles and then every 4 Weeks)

	Screening	Cycle = 21 days (3 weeks)										Cycle = 28 days (4 weeks)	End-of-Treatment	Follow-up Visits				Details in CSP Section or Appendix
		Cycle 1				Cycle 2			Cycle 3		Cycle 4 to 10	Cycle 11 onwards						
Week	-4 to -0	1	1	2	3	4	5	6	7	9	10-32	33+		30-days (±7 days) after last treatment	90-days (±7 days) after last treatment	Progress-ion-free survival[a] (Every 12 weeks [±7 days])	Survival 90 days (Every 3 months (±7 days) after last treatment, until final DCO)	
Day (visit window ±3 days from Cycle 2, Day 1 onwards)	-28 to 0	1	2	8	15	1	8	15	1	15	1	1						
Survival status/subsequent cancer therapy																	X	8.2.10.3
ePRO (BPI-SF)[h]		X				X			X		X	X	X	X		X		8.2.9
ePRO (FACT-P)[h]		X				X			X		X	X	X	X		X		8.2.9
Study intervention administration																		
AZD4635 dispensed (daily dosing)		→				→			→		→							6.2.1
Diary review		X				X			X		X	X						6.2.1, 6.4
Durvalumab 1500 mg IV		X				X			X		X	X						6.2.2.1

Appendix B Schedule of Activities for Arm B (AZD4635 plus Durvalumab and Cabazitaxel every 3 Weeks for First 10 Cycles and then every 4 Weeks)

	Screening	Cycle = 21 days (3 weeks)										Cycle = 28 days (4 weeks)	End-of-Treatment	Follow-up Visits				Details in CSP Section or Appendix
		Cycle 1				Cycle 2			Cycle 3		Cycle 4 to 10	Cycle 11 onwards						
Week	**-4 to -0**	**1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**9**	**10-32**	**33+**		**30-days (±7 days) after last treatment**	**90-days (±7 days) after last treatment**	**Progression-free survival[a] (Every 12 weeks [±7 days])**	**Survival 90 days (Every 3 months (±7 days) after last treatment, until final DCO)**	
Day (visit window ±3 days from Cycle 2, Day 1 onwards)	**-28 to 0**	**1**	**2**	**8**	**15**	**1**	**8**	**15**	**1**	**15**	**1**	**1**						
Cabazitaxel 20 mg/m^2 or 25 mg/m^2 (per locally approved label) plus prednisone 10 mg PO plus primary G-CSF prophylaxis[i]		X				X			X		X							6.2.3.1

a Participants will be followed up every 12 weeks (±1 week) starting from the last date of the last tumour response assessment until either: objective PD has been confirmed, withdrawal of consent, until the primary DCO for the arm, or until the study is terminated by the Sponsor.

b Routine clinical and safety assessments may be done 1 day prior to each visit, if required.

c During the study, tests for active COVID-19 infection may be prescribed, if required, and in accordance with local guidelines.

d An echocardiogram or multiple-gated acquisition (MUGA) scan obtained in the 6 months prior to screening will be acceptable unless there has been a change in the participant's cardiac status, in which case this will be repeated. If there is no echocardiogram or MUGA within 6 months prior to study enrollment, this will be performed at screening. Additional assessments for echocardiogram or MUGA during the study will be determined as clinically indicated based on the current available data.

e Haematology will include a full blood count with differential blood counts.

f Per Protocol Appendix G, while PET scans are not considered adequate to measure lesions, PET-CT scans may be used providing that the measures are obtained from the CT scan and the CT scan is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast).

g At least half of the participants should have RECIST v1.1 measurable disease at baseline (ie, at least 40 participants enrolled and assigned to study treatment in Arm B, including approximately 15 participants at the time of interim analysis).

h The PRO instruments will be administered and completed at the start of each visit.

i Participants should be observed closely for hypersensitivity reactions especially during the first and second infusions, as per the local cabazitaxel label. Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of cabazitaxel, thus facilities and equipment for the treatment of hypotension and bronchospasm should be available (Protocol Section 6.7.3). Dose modifications should be made if participants experience the following adverse reactions per Protocol Table 12.

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