- **Protocol number:** D8731C00002
- **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)
- **NCT number:** NCT04495179
- **Version number:** 3.0
- **Date of the document:** 24 Nov 2020

Clinical Study Protocol	
Study Intervention	AZD4635
Study Code	D8731C00002
Version	3.0
Date	24 November 2020

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)

Sponsor: AstraZeneca AB

Legal Registered Address: 151 85 Södertälje, Sweden

Regulatory Agency Identifier Number(s)

Investigational New Drug (IND) Number: 138166

European Clinical Trials Database (EudraCT) number: 2020-000209-10

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

Protocol Number: D8731C00002

Amendment Number: 2

Study Intervention: AZD4635

Study Phase: II

Short Title: Phase II two-arm study of AZD4635 in combination with durvalumab and in combination with cabazitaxel and durvalumab in patients with mCRPC

Study Acronym: **AARDVARC, A_{2A}R** inhibitor and **DurV**alumab **A**ssessment of **R**esponse in **C**RPC

Medical Monitor Name and Contact Information will be provided separately

International co-ordinating investigator: PPD

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 2 (Global)	24-Nov-2020
Amendment 1 (Global)	07-Sep-2020
Original Protocol	31-Jan-2020

The Protocol Amendment Summary of Changes Table is provided below for the current amendment and in Appendix N for previous amendments.

Amendment 2, 24-November-2020

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the council of the European Union.

Overall Rationale for the Amendment:

The global protocol was amended due to the Sponsor's decision to close enrolment in Arm A. A few additional corrections and clarifications were included in this amendment.

A summary of changes and the rationale for each change are tabulated below.

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
1.1 Synopsis	Alignment to updates made in Sections 2, 3, 4, and 9.	These edits were made for consistency with the updates made to main protocol sections.	Substantial
	Site locations were updated.	Revisions were made to align with updated assumptions.	Substantial
1.2 Schema	A footnote was added to Figure 1 (study design) to describe decision to stop enrolment in Arm A.	The footnote was for consistency with the updates made to main protocol sections.	Substantial
1.3 Schedule of Activities	Paired tumour biopsies were edited in both Tables 1 and 2 to add samples at the visits described in Section 8.6.2.1.	These edits were made for consistency with Section 8.6.2.1.	Non-substantial
	In Tables 1 and 2, a footnote was added to clarify when PET-CT scans may be used.	Information provided in Appendix G was added as a footnote for clarity.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	In Table 2 (Arm B), the number of participants requiring intensive PK sampling was increased from 6 to 12 evaluable participants.	These edits were made for consistency with updates made in Section 8.5.1.	Substantial
	In Table 2 (Arm B), a footnote was added to specify the number of participants with RECIST v1.1 measurable disease at baseline to be enrolled and assigned to study treatment in Arm B	These edits were made for clarity and in alignment with the main sections of the protocol.	Non-substantial
2 Introduction, 4.1 Overall Design, and 4.3 Justification for Dose	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).	As of November 2020, the Sponsor stopped enrolment in Arm A following decisions at the program level, not related to any safety issues.	Substantial
3 Objectives and Endpoints	CCI [redacted]	CCI [redacted]	Substantial
4.1.1 Safety Review Committee	The safety review committee (SRC) decision will be shared with all investigators, but statement that this should occur prior to further dosing of	This revision was made for consistency with the process described in the protocol.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	participants on Arm B was deleted.		
4.4 End of Study Definition	The DCO for primary analysis and reporting defined for Arm B will be used for both treatment arms.	As enrolment in Arm A stopped, the DCO previously defined for Arm A can no longer be completed.	Substantial
	For Arm B, the DCO was changed to when approximately 60% of events (death or progression) occur.	A 60% maturity is considered sufficient to evaluate the updated decision criteria, which is what the sample size is based on.	Substantial
5.1 Inclusion Criteria, 5.2 Exclusion Criteria	For inclusion criterion #8 and exclusion criterion #6, the minimum creatinine clearance for eligibility was lowered from 50 to 40 ml/min	Available data show that all study drugs have only minimal renal clearance. No significant renal toxicity has been seen for AZD4635. The proposed threshold is also in line with the guidance for durvalumab and cabazitaxel.	Substantial
	Exclusion criteria #5 and #11 were edited to remove duplicate information.	These edits were made to improve clarity, but do not change the criteria.	Non-substantial
	For exclusion criterion #29, ejection fraction was replaced by left ventricular ejection fraction.	These edits were made to improve clarity, but do not change the criteria.	Non-substantial
6.2.1 AZD4635	Dosing instructions in case of vomiting were added.	The instructions were added in the protocol for completeness, in alignment with the dosing instruction provided to each participant.	Non-substantial
6.3 Measures to Minimise Bias: Methods for Assigning Treatment Groups	The section was updated to indicate that assignment depends on which treatment arm is open and to clarify that stratification is to ensure a sufficient number of participants are enrolled in each stratum of Arm B.	As enrolment in Arm A stopped, the description of treatment assignment was revised accordingly.	Substantial
6.7 Dose Modification	The maximum duration of 4 weeks of treatment interruption in case of immune-mediated toxicity was removed.	Recovery from immune-mediated adverse events may require more than 4 weeks of treatment interruption for full steroid treatment and taper.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
7.3 Lost to Follow-up	Text regarding the collection of information on the vital status of participants lost to follow-up was added.	These edits were made to clarify that the vital status of participants lost to follow-up should be collected.	Substantial
8.1.1 Tumour Assessments with RECIST v1.1	Text was added to clarify when PET-CT scans may be used.	Information provided in Appendix G was added in the section for clarity.	Non-substantial
8.5.1 Pharmacokinetics	The number of Arm B participants requiring intensive PK sampling was increased from 6 to 12 evaluable participants.	Six participants were added to better evaluate the PK effects of cabazitaxel added to the combination of AZD4635 + durvalumab.	Substantial
9.2 Sample Size Determination.	Calculation of sample size for Arm A was removed.	As enrolment in Arm A stopped, calculation of sample size is no longer relevant.	Substantial
	Calculation of sample size for Arm B was updated to reflect updated DCO, target value for the decision criteria and current recruitment estimates.	Revisions were made to align with updated assumptions.	Substantial
9.4.1 General Considerations, 9.4.1.2 Secondary Endpoints	Summary tables will not be produced for Arm A Data from Arm A will be listed only.	As enrolment in Arm A stopped, too few participants will be enrolled to produce meaningful analyses.	Substantial
9.5 Interim Analysis	The futility interim analysis for Arm A was removed. A futility interim analysis was added for Arm B.	As enrolment in Arm A stopped, the futility interim analysis is no longer required for Arm A. A futility interim analysis was added in Arm B to decide further enrolment in Arm B after reviewing data from approximately 30 evaluable participants (including approximately 15 participants with RECIST v1.1 measurable disease at baseline). This is due to the limited data available for this combination.	Substantial
Appendix K Fact-P Version 4	Missing page 2 in the appendix was added.	Correction.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Appendix L COVID-19 Specifics	The requirements for Investigational Product administration in case of remote visit were clarified.	These clarifications were provided to ensure the remote location is appropriate to safely perform the IP administration.	Substantial
General formatting and minor editing	The format of table numbering was changed back to format used in the initial protocol. Minor formatting and editorial changes were made for corrections or to ensure alignment with updated sections.	Correction and editing	Non-substantial

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol 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)

Short Title: Phase II two-arm study of AZD4635 in combination with durvalumab and in combination with cabazitaxel and durvalumab in patients with mCRPC

Rationale: Although novel hormonal agents (NHA) have changed the landscape of treatment for metastatic castrate-resistant prostate cancer (mCRPC), for patients who have progressed with NHA and docetaxel, there remain limited therapeutic options. While immunotherapy has led to impressive responses in a subset of patients with immunologically "activated" tumors, this approach has shown little progress in mCRPC. AZD4635 has shown clinical activity in mCRPC and appears to have increased efficacy in combination with anti-PD-L1 in prostate cancer due to increased immune activation compared to single agent AZD4635 based on the results of the ongoing Phase I study D8730C00001. At the data cut-off (DCO) of 02 December 2019, 8 subjects have achieved objective response (OR) per Response Evaluation Criteria in Solid Tumours (RECIST) v1.1. Two subjects (durvalumab combination) had complete responses and 6 subjects had partial responses (monotherapy [n = 2] and durvalumab combination [n = 4]). Participants with an OR (CR+PR) have had durations of response that ranges from 2.30 to 25.82 months with several ongoing response at the DCO.

The combination of the checkpoint inhibitor pembrolizumab (anti-PD-1) and docetaxel has been investigated in the KEYNOTE 365 study where the checkpoint inhibitor was added to the standard-of-care (SOC) chemotherapy. It has been reported that pembrolizumab alone leads to a relatively low response rate of ~5% and percentage of participants who had a Prostate-Specific Antigen (PSA) decline of at least 50 percent (%) from baseline, i.e., PSA_{50} of 11% (KEYNOTE-199) (Antonarakis et al 2019). In KEYNOTE 365, an ORR of 14% (5/36) and PSA_{50} of 31% (22/71) were reported with the most notable result being a median radiographic progression-free survival (rPFS) of 8.3 months (Massard et al. 2019) which is longer than that reported with single-agent docetaxel (3.9 months [Rathkopf et al. 2018]). Additionally, the recently published CARD study (de Wit et al. 2019) demonstrated an imaging-based median PFS of ~8.2 months for the cabazitaxel arm in a post-NHA, post-docetaxel unselected mCRPC participant population.

We hypothesise that AZD4635 combined with the checkpoint inhibitor (anti-PD-L1) durvalumab and cabazitaxel will lead to an increased rPFS in the post-docetaxel setting by decreasing the immunosuppressive environment response and counteracting the effects of adenosine (ADO) which can limit the anti-PD1/PDL1.

Objectives and Endpoints

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 until radiographic progression as assessed by the Investigator per RECIST v1.1 (soft tissue) and Prostate Cancer Working Group 3 (PCWG3) criteria (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.

Objectives	Endpoints/Variables
• To determine the efficacy of AZD4635 plus durvalumab and separately of AZD4635 plus durvalumab plus cabazitaxel, by assessment of ORR in participants with mCRPC.	• Confirmed ORR, defined as the percentage of participants with a confirmed Investigator-assessed response of 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 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 of AZD4635 plus durvalumab plus cabazitaxel, by assessment of 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 concentrations 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 signature in high and low subgroups.	• rPFS, defined as the time from first dose until 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.

Objectives	Endpoints/Variables
• 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, 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.

For Exploratory objectives and endpoints/variables see Section 3 of the protocol.

Overall 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). Participants in each arm will be stratified by the presence of measurable soft tissue metastasis (per RECIST v1.1, Appendix F) or bone-only metastasis (per Prostate Cancer Working Group 3 [PCWG3 criteria, Appendix H]). There will be no formal comparisons between treatment arms. Secondary endpoints include; safety, OS, confirmed ORR, DoR, confirmed PSA_{50} 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 (e.g., abiraterone acetate, enzalutamide, apalutamide and/or darolutamide), and one or more taxanes, or participants who are taxane ineligible. 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 PWCG3) and ongoing androgen deprivation with serum

testosterone <50 ng/mL.

Participants will be allocated to one of the following treatment arms:

Arm A: AZD4635 ([redacted] 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.

or

Arm B: AZD4635 ([redacted] mg PO daily) plus durvalumab (1500 mg IV every 3 weeks [Q3W]) plus cabazitaxel (20 or 25 mg/m^2 IV Q3W as per the local prescribing guidelines [n = 80]).

Participants in Arm B will receive cabazitaxel chemotherapy as per the local label. This will start approximately 1 hour (or up to a maximum of 2 hours) after the end of the durvalumab infusion. Cabazitaxel will be administered as per the local prescribing guidelines for a maximum of 10 cycles. After cycle 10 durvalumab + AZD4635 will be administered Q4W to harmonise with the Arm A treatment cycle length.

Arm B participants must receive premedication to manage cabazitaxel-associated reactions (hypersensitivity or other) which include:

- Prednisone (10 mg daily continuously [or equivalent steroid]) for the duration of cabazitaxel administration
- Primary G-CSF prophylaxis (G-CSF should be administered according to the product label and institutional standards.)

An archival tumour sample is required or the participant must be willing to undergo a baseline tumour biopsy (see Section 8.6.1.3). The collection of paired tumour biopsies will be requested during the study, however this is optional (see Section 8.6.2.1).

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. Note: 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).

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. 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 4.1.1).

The patient reported outcome (PRO) instruments, a BPI-SF (see Appendix J) and FACT-P (see Appendix K) will be administered to all participants. These two instruments will be used to assess pain and quality of life in study participants and to determine the time to pain progression as well as the change in maximal pain (see Section 3). These will be measured as shown in Table 1 and Table 2.

Disclosure Statement: This is a parallel group treatment study with 2 arms that is open-label.

Number of Participants: Approximately 80

The two arms will enroll participants with metastatic disease documented by either bone lesions on bone scan or soft tissue disease that is evaluable for assessment. 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 will enroll and assign to study treatment approximately 80 participants. At least 40 participants with RECIST v1.1 measurable disease at baseline will be enrolled and assigned to study treatment in Arm B, and the remainder of participants in the arm (n = 40) may have bone-only disease or measurable disease. The primary analysis, rPFS, will be assessed, and is defined as the time from first dose to radiographic progression as determined by the Investigator per RECIST v1.1 for soft tissue disease or PCWG3 for bone disease or death from any cause, whichever occurs first. Overall survival, ORR, DoR, and PSA_{50} response, and time to pain progression will also be evaluated for efficacy.

Note: "Enrolled" means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but, are not assigned in the study, are considered "screen failures", unless otherwise specified by the protocol.

A master log of all consented participants will be maintained at the site and will document all screen failures defined in Section 5.4). During the study, tests for active Coronavirus disease of 2019 (COVID-19) infection may be prescribed, if required, and in accordance with local guidance.

Locations: Up to 50 global sites to recruit over approximately 18 months in the United States, Europe and the Asia/Pacific region.

Intervention Groups and Duration:

Arm A: AZD4635 capsule CCI mg PO daily + durvalumab 1500 mg IV 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. 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).

Arm B (n = ~80):
AZD4635 capsule [redacted] mg PO daily + durvalumab 1500 mg IV Q3W + cabazitaxel 20 mg/m^2 IV Q3W or 25 mg/m^2 IV Q3W (as per local prescribing guidelines)

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. Participants may continue to receive study intervention until confirmed objective disease progression as assessed by the Investigator, or unacceptable toxicity or for as long as they do not meet any other discontinuation criteria. Once participants have been discontinued from study intervention, other treatment options will be at the discretion of the Investigator.

In this protocol AZD4635, durvalumab and cabazitaxel are all referred to as either study drugs, study interventions, investigational products (IPs), or investigational medicinal products, and these terms are used interchangeably.

Statistical methods

As of November 2020, the Sponsor stopped enrolment in Arm A following decisions at the program level. For Arm A, data will be listed only.

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 defined as the time from first dose until radiographic progression as assessed by the Investigator per RECIST v1.1 (soft tissue) and PCWG3 (bone) or death from any cause, whichever comes first. For Arm B, the analysis will be descriptive, including summaries from the Kaplan-Meier curve. It is anticipated that the study accrual period will be approximately 14 months for Arm B. [redacted]
Eighty participants will provide an estimate of the median PFS. Confidence intervals (CI) will be constructed around the median PFS, to enable decisions to be made about the likely success of future studies in this population.

[redacted]

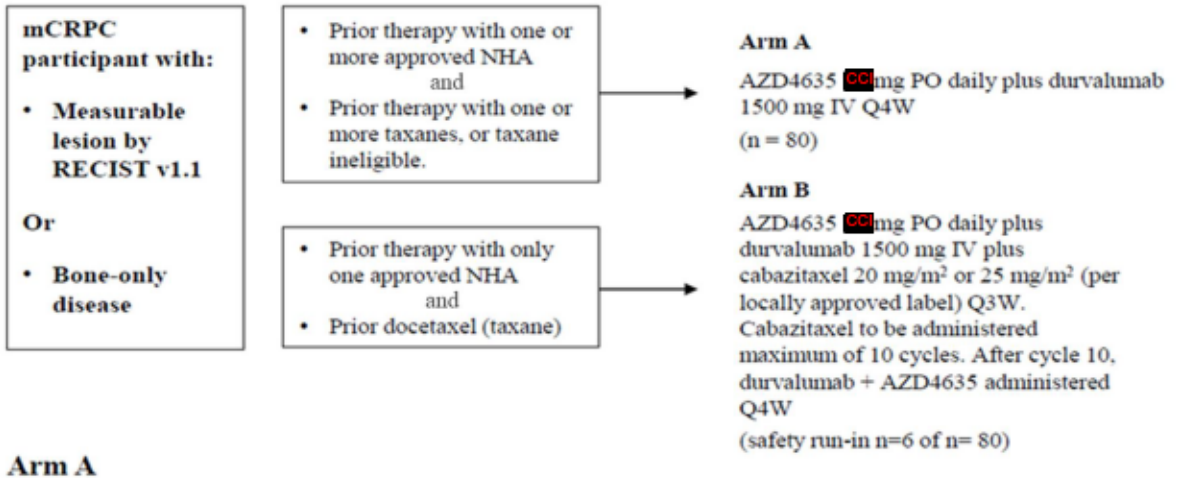
[redacted]

Secondary endpoints include: safety, OS, ORR, DoR, PSA_{50} response, time to pain progression, and PK. The analysis will be descriptive, and summaries will be presented for Arm B. The primary endpoint (ie, rPFS) will also be summarised by ADO signalling gene expression in high and low subgroups in Arm B.

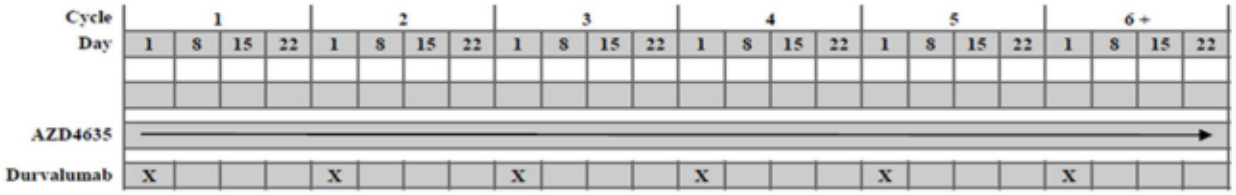
Given the limited data available with the triplet combination, a futility interim analysis is planned for Arm B based on PSA_{50} response and will be triggered according to the following: after approximately n = 30 dosed participants for the arm have had the opportunity for sample collection for PSA 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. Further details will be provided in the SAP. 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 up. 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 PSA_{50} 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.

1.2 Schema

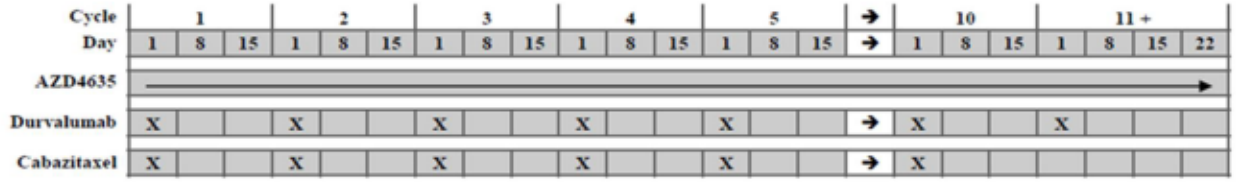
Figure 1 Study design



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 Schedule of Activities

Table 1 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
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

Table 1 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
Durvalumab pre-infusion blood sample for anti-drug antibody		X			X				X (C4 & C7 only)			X			8.5.2, Table 20

Table 1 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						
Biomarker assessments															
CCI															
CCI															
CCI															8.7

Table 1 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						
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]
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															
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.

[redacted]

f Per 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.

Table 2 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

Table 2 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

Table 2 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**						
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

Table 2 **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																		
Adenosine (ADO) signalling gene expression	X	X																8.6.1.1
CCI [redacted]	[redacted]	[redacted]				[redacted]			[redacted]		[redacted]	[redacted]	[redacted]					[redacted]
[redacted]		[redacted]		[redacted]		[redacted]			[redacted]		[redacted]	[redacted]		[redacted]				[redacted]
[redacted]	[redacted]	[redacted]			[redacted]		[redacted]		[redacted]	[redacted]	[redacted]							[redacted]
[redacted]	[redacted]																	[redacted]

Table 2 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						
[redacted]	[redacted]	[redacted]			[redacted]								[redacted]					[redacted]
CCI [redacted]																		
CCI [redacted]		[redacted]																CCI
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]

Table 2 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**						
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

Table 2 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 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 (Section 6.7.3). Dose modifications should be made if participants experience the following adverse reactions per Table 12.

2 INTRODUCTION

AZD4635 is a novel adenosine$_{2A}$ receptor ($A_{2A}R$) antagonist agent that acts against cancer by blocking adenosine-mediated $A_{2A}R$ signalling in tumour-infiltrating immune cells. $A_{2A}R$ signalling suppresses effector T and natural killer cell function and increases the function of regulatory T-lymphocyte (T cells) and myeloid derived suppressor cells. AZD4635-mediated $A_{2A}R$ blockade is hypothesised to make the tumour microenvironment (TME) less immunosuppressive, thus improving anti-tumour immune responses. Modulation of the TME with drugs that decrease adenosine (ADO) levels or inhibit the $A_{2A}R$ may reverse these effects and enable the host to mount an effective anti-tumour immune response, even in tumour types that are not typically responsive to immune checkpoint inhibitors.

Durvalumab is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody (mAb) that blocks the interaction of programmed cell death ligand 1 (PD-L1) with programmed cell death protein 1 (PD-1) on T cells and with cluster of differentiation 80 (CD80) (B7-1) on immune cells and is engineered to reduce antibody-dependent cell-mediated cytotoxicity and complement activation. *In vitro* studies have demonstrated that durvalumab antagonizes the inhibitory effect of PD-L1 on primary human T cells, resulting in the restored proliferation of interferon gamma (IFN-γ), and *in vivo* studies have shown that durvalumab inhibits tumour growth in xenograft models via a T cell-dependent mechanism (Stewart et al. 2015). Based on these data, durvalumab is expected to stimulate the patient's anti-tumour immune response by binding to PD-L1 and shifting the balance toward such a response.

Cabazitaxel (Jevtana®) a microtubule inhibitor was approved by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in 2010 and 2011, respectively, for the treatment of patients with mCRPC previously treated with docetaxel. The recommended cabazitaxel approved dose by both agencies is 25 mg/m^2 administered Q3W in combination with prednisone 10 mg PO daily.

Cabazitaxel approval is based on results from the TROPIC trial (NCT00417079) in which participants with hormone-refractory metastatic prostate cancer either measurable by RECIST criteria or with non-measurable disease with rising PSA levels or with new lesions were randomized (n = 755) to receive either cabazitaxel 25 mg/m^2 IV Q3W for a maximum of 10 cycles with prednisone 10 mg PO daily (n = 378), or mitoxantrone 12 mg/m^2 IV Q3W for 10 cycles with prednisone 10 mg PO daily (n = 377) for a maximum of 10 cycles. Investigator-assessed tumour response of 14.4% (95% confidence interval [CI]: 9.6-19.3) was higher for participants in the cabazitaxel arm than for participants in the mitoxantrone arm (4.4% [95% CI: 1.6-7.2]), p = 0.0005.

The TROPIC trial demonstrated that cabazitaxel is the first treatment to prolong survival in mCRPC since the approval of docetaxel (Villanueva et al. 2011). The FDA and EMA approved cabazitaxel in June 2010 and January 2011, respectively, based on this data. On

14 September 2017, the FDA approved a lower dose of cabazitaxel for mCRPC (20 mg/m^2) Q3W in combination with prednisone. The PROSELICA trial (NCT0130850) randomised mCRPC participants (n = 1200) to either cabazitaxel 25 mg/m^2 IV Q3W (n = 602) or 20 mg/m^2 IV Q3W (n = 598). Overall survival was the major efficacy outcome. Participants on cabazitaxel 20 mg/m^2 had an estimated median OS of 15.1 months and participants on cabazitaxel 25 mg/m^2 had median OS of 15.9 months, the observed hazard ratio (HR) of OS was 1.042 (97.78% CI: 0.886, 1.224). No notable difference in OS was in subgroups based on the stratification factors of ECOG performance status score, measurability of disease, or region.

This Phase II international, open-label, two-arm, non-randomised study will evaluate the efficacy, safety and tolerability and PK of AZD4635 given in combination with durvalumab, and in combination with durvalumab plus cabazitaxel, in genetically unselected patients with mCRPC previously treated with a NHA and docetaxel (or one or more taxanes or who are taxane ineligible [depending on treatment arm]). Participants in each arm will be stratified by the presence of measurable soft tissue metastasis (per RECIST v1.1, Appendix F) or bone-only metastasis (per PCWG3 criteria, Appendix H). There will be no formal comparisons between treatment arms. Participants with mCRPC will be allocated to one of the following treatment arms:

Arm A: AZD4635 (CCI mg PO daily) plus durvalumab (1500 mg IV 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. 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).

or

Arm B: AZD4635 (CCI mg PO daily) plus durvalumab (1500 mg IV Q3W)
plus cabazitaxel (20 or 25 mg/m^2 IV Q3W as per the local prescribing guidelines) (n = 80)

Participants in Arm B must receive the following premedication to manage cabazitaxel-associated reactions (hypersensitivity or other):

- Prednisone (10 mg daily continuously [or equivalent steroid]) for the duration of cabazitaxel administration
- Primary G-CSF prophylaxis

Participants in Arm B will receive cabazitaxel chemotherapy as per the local label. This will start approximately 1 hour (or up to a maximum of 2 hours) after the end of the durvalumab infusion. Cabazitaxel will be administered as per the local prescribing guidelines for a maximum of 10 cycles. After cycle 10 durvalumab + AZD4635 will be administered Q4W to

harmonise with the Arm A treatment cycle length.

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 based on RECIST v1.1 or the presence of bone lesions per PWCG3, and have ongoing androgen deprivation with serum testosterone <50 ng/mL. An archival tumour sample or baseline tumour biopsy is required. The collection of paired tumour biopsies will be requested during the study; however, this is optional.

At baseline eligible participants must have RECIST-measurable disease (target lesions) or bony non-measurable disease (non-target bone lesions) (Appendix F). In addition, PSA will be evaluated at the start of each cycle as per PCWG3.

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. 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. A safety assessment to determine the safety and tolerability of this combination will be conducted by the SRC once the first 6 participants have completed a safety run-in period of at least 1 cycle (see Section 4.1.1). Cabazitaxel will be discontinued after 10 cycles, and AZD4635 and durvalumab may be continued every 4 weeks.

Participants may continue to receive study intervention until confirmed objective disease progression as assessed by the Investigator, or until they suffer from unacceptable toxicity or for as long as they do not meet any other discontinuation criteria. Once participants have been discontinued from study treatment, other treatment options will be explored at the discretion of the Investigator.

The two arms will enrol participants with metastatic disease (see Figure 1). As of November 2020, the Sponsor stopped enrolment in Arm A. Arm B will enroll and assign to study treatment approximately 80 participants. At least 40 participants with RECIST v1.1-measurable soft-tissue disease at baseline will be enrolled and assigned to study treatment in Arm B, and the remainder of participants in the arm (n = 40) may have bone-only disease (on bone scan [per PWCG3]) or measurable disease. The primary objective of the study is to assess rPFS. rPFS is defined as the time from first dose to radiographic progression as determined by the Investigator according to RECIST v1.1 for soft tissue disease or PCWG3 for bone disease or death from any cause, whichever occurs first. Overall survival and the ORR, DoR, PSA_{50} response, and time to pain progression will also be evaluated for efficacy.

A futility interim analysis is planned for Arm B based on PSA_{50} response for approximately n = 30 dosed participants. 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.

For detailed descriptions of the chemistry, pharmacology, efficacy, and safety of AZD4635 and durvalumab, refer to the respective Investigator's Brochures (IBs). For detailed descriptions of the chemistry, pharmacology, efficacy, and safety of cabazitaxel, refer to the respective product labels, either the US prescribing information or the EU Summary of Product Characteristics (SmPC).

2.1 Study Rationale

Although novel hormonal agents (NHA) have changed the landscape of treatment for mCRPC, for patients who have progressed with NHA and docetaxel, there remain limited therapeutic options. While immunotherapy has led to impressive responses in a subset of patients with immunologically "activated" tumours, this approach has shown little progress in mCRPC. AZD4635 appears to have increased efficacy in combination with anti-PD-L1 in patients with mCRPC who have exhausted standard of care options due to increased immune activation compared to single agent AZD4635 based on the results of the ongoing Phase I study D8730C00001. At the data cut-off (DCO) of 02 December 2019, 8 subjects had achieved objective response (OR) per RECIST v1.1. Two subjects (durvalumab combination) had complete responses and 6 subjects had partial responses (monotherapy [n = 2] and durvalumab combination [n = 4]). The participants with an OR (CR or PR) have had a duration of response that ranged from 2.30 to 25.82 months with several participants' durations ongoing at the DCO.

The combination of the checkpoint inhibitor pembrolizumab (anti-PD-1) and docetaxel has been investigated in the KEYNOTE 365 study where the checkpoint inhibitor was added to the standard-of-care (SOC) chemotherapy. It has been reported that pembrolizumab alone leads to a relatively low response rate of ~5% and PSA_{50} of 11% (KEYNOTE-199) (Antonarakis et al 2019). In KEYNOTE 365, an ORR of 14% (5/36) and PSA_{50} of 31% (22/71) were reported with the most notable result being a median radiographic progression-free survival (rPFS) of 8.3 months (Massard et al. 2019) which is longer than that reported with single-agent docetaxel (3.9 months [Rathkopf et al. 2018]). Additionally, the recently published CARD study (de Wit et al. 2019) demonstrated an imaging-based median PFS of ~8.2 months for the cabazitaxel arm in a post-NHA, post-docetaxel unselected mCRPC participant population.

While the KEYNOTE-365 provides early evidence to support the combination of chemotherapy and checkpoint inhibition in mCRPC, we hypothesise that AZD4635 combined with the checkpoint inhibitor (anti-PD-L1) durvalumab and cabazitaxel will lead to an

increased rPFS in the post-docetaxel setting by decreasing the immunosuppressive environment and counteracting the effects of ADO which can limit the anti-PD1/PDL1 response.

2.2 Background

Prostate cancer is the second most common cancer in men. In 2018, over 1.2 million new cases of prostate cancer were diagnosed worldwide and there were 350,000 deaths due to the disease (Bray et al. 2018). For men requiring systemic therapy, hormonal therapy has been the mainstay. Once the disease becomes resistant to hormonal therapy, the disease is known as castration-resistant prostate cancer (CRPC). Treatment for both metastatic and non-metastatic prostate cancer has evolved over the past 15 years. In 2004, the development of a docetaxel regimen for the treatment of CRPC was the first chemotherapy to show a survival benefit and subsequently became the standard-of-care chemotherapy for CRPC. A regimen of docetaxel given Q3W had a median OS of 18.9 months (95% CI 1417.0-21.2), which was greater than the survival of 16.5 months (95% CI 14.4 – 18.6 months) for a mitoxantrone control arm. The hazard ratio (HR) for death was 0.76 (95% CI 0.62-0.94, p = 0.009) for docetaxel compared to mitoxantrone (Tannock et al. 2014). However, many of the treatments for prostate cancer, including docetaxel and cabazitaxel for mCRPC, are not suitable for all patients and many patients are refractory to these treatments so alternative treatment options are needed.

New hormonal agents have become standard of care for mCRPC and include enzalutamide and abiraterone plus prednisone. Enzalutamide, a targeted androgen-receptor inhibitor that blocks the binding of androgen to the androgen receptor, translocation to the nucleus, and DNA binding (Tran et al. 2009), was approved for the first-line treatment of patients with mCRPC. Abiraterone, a selective inhibitor of 17 α-hydroxylase/C17,20-lyase (CYP17), was also approved in combination with prednisone for the treatment of mCRPC in the first-line setting (Ryan et al. 2013a, Ryan et al. 2013b).

AZD4635 is being developed as monotherapy and as an immuno-oncology agent in combination with durvalumab (anti-PD-L1) and durvalumab plus oleclumab (cluster of differentiation 73 [CD73] monoclonal antibody), exploiting complementary immune-related mechanisms to broaden and deepen clinical responses. AZD4635 has shown activity in a variety of tumour types, with encouraging data being seen for the combination AZD4635 and durvalumab in the Phase I study. As stated previously, this Phase II study will evaluate the efficacy, safety and tolerability of the combination of AZD4635 and durvalumab and the combination of AZD4635 with durvalumab and cabazitaxel. CCI [redacted]

Durvalumab (IMFINZI®) is FDA-approved in patients with bladder urothelial carcinoma who

have disease progression during or following platinum-containing chemotherapy and in patients who have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. Durvalumab is also approved in patients with NSCLC whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy. Durvalumab, in combination with etoposide and either carboplatin or cisplatin, is also approved for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC) (IMFINZI® US Prescribing Information).

Durvalumab is approved by the European Medicines Agency (EMA) as monotherapy for the treatment of locally advanced, unresectable NSCLC in adults whose tumours express PD-L1 on ≥1% of tumour cells and whose disease has not progressed following platinum-based chemo-radiation therapy (IMFINZI®, EU SmPC).

Although NHAs have changed the landscape of treatment for mCRPC, for patients who have progressed on NHAs and docetaxel, there remain limited therapeutic options. While immunotherapy has led to impressive responses in a subset of patients with immunologically 'activated' tumours, this approach has shown little progress in mCRPC. The addition of AZD4635 to anti-PD/PDL1 therapy or the combination of anti-PDL1 plus cabazitaxel may lead to an improvement in rPFS in these patients.

2.2.1 Benefit/Risk Assessment

As of December 2019 approximately 300 patients with advanced cancer had been treated with AZD4635, either alone or in combination with another cancer drug. As of 02 December 2019 (date of DCO) in the ongoing study D8730C00001, 84 subjects (monotherapy cohorts n = 21 and combination cohorts n = 63) had been enrolled in the Phase 1a dose escalation cohorts. The second segment of the study (Phase 1b) consists of dose expansion cohorts in tumor types for which there is a rationale for potential efficacy of the study treatment. As of 02 December 2019, 191 subjects (117 monotherapy cohorts and 74 combination cohorts) had been dosed in Phase 1b. A pooled dataset for AZD4635 monotherapy and AZD4635 combination cohorts was generated for the 22 treatment cohorts to enhance the review process.

The median age for the monotherapy participants = 71 years and for the combination = 70 years; ECOG performance status was 0-1 in 99% of participants. The median number of prior treatment regimens at baseline was 5 (range = 1-10) for all participants.

Seventy participants were evaluable for tumour response (monotherapy = 33, combination = 37). RECIST v1.1 responses were confirmed in 8 participants: (monotherapy=ORR 6.1% [2 PRs]) and (combination = 16.2% [2CRs, 4PRs]). The median PFS for the monotherapy cohort was 13.6 weeks (95% CI, 7.1-15.3) and 14.9 weeks (95% CI, 13.3-29.3) for the combination cohort.

PSA response (defined as ≥ 50% decrease from baseline) was observed in monotherapy = 6.4% (3/47 participants; 95% CI, 1.3-17.5%) and combination = 20% (9/45 participants; 95% CI, 9.6-34.6%).

Most common related AEs (>10%) were nausea, vomiting, fatigue, dizziness, decreased appetite, and diarrhoea. Events of nausea and vomiting seen with AZD4635 treatment in Phase I study D8730C00001 were reported in 58.8% of AZD4635 treated subjects (AZD4635 IB). These events are generally mild to moderate (CTCAE grade 1 or 2) severity, intermittent and manageable on continued treatment. The first onset generally has an onset in the first week of treatment for both nausea and vomiting.

For information on all identified and potential risks with durvalumab and AZD4635 refer to the current versions of the Investigator Brochures (IB) for each intervention.

Adverse reactions and laboratory abnormalities occurring in greater than 10% of participants in clinical trials of cabazitaxel were neutropenia, anaemia, leukopenia, thrombocytopenia, diarrhoea, fatigue, nausea, vomiting, constipation, asthenia, abdominal pain, haematuria, back pain and anorexia. Grade 3-4 infections were reported in 20% of participants on the 25 mg/m^2 dose arm and 10% of participants on the 20 mg/m^2 arm. Febrile neutropenia occurred in 9% of participants on the higher dose arm and 2% of participants on the 20 mg/m^2 arm. The most common reasons for dose discontinuation were fatigue and haematuria.

Refer to the US prescribing information or the EU SmPC for details on current prescribing information.

After approximately 6 participants on the arm with AZD4635 plus durvalumab plus cabazitaxel have been enrolled and treated for at least one cycle, we will review the safety information for the AZD4635 plus durvalumab plus cabazitaxel treatment arm, as well as available PK data, particularly because the combination of AZD4635 plus durvalumab plus cabazitaxel has not been evaluated previously. The SRC may consider reducing the AZD4635 dose to [redacted] mg PO daily from [redacted] mg after the safety review if there are safety and tolerability concerns (see Section 4.1.1). Risk considerations in view of the potentially relapsing COVID-19 pandemic are detailed in Appendix L.

3 OBJECTIVES AND ENDPOINTS

Table 3 Objectives and Endpoints/Variables

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 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 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

Objectives	Endpoints/Variables
	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 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 of AZD4635 plus durvalumab plus cabazitaxel, by assessment of 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 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, the FAPSI-8 as derived from 8 items within the FACT-P, and the PCS, as derived from

Objectives	Endpoints/Variables
	the 12 items in the prostrate-specific module of the FACT-P.
CCI	
• CCI	• CCI
• CCI	• CCI
• CCI	• CCI
• CCI	• CCI

Objectives	Endpoints/Variables
• CCI	• CCI
• CCI	• CCI
• CCI	• CCI
• CCI	CCI

4 STUDY DESIGN

4.1 Overall 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, Appendix F) or bone-only metastasis (per PCWG3 criteria, Appendix H). There will be no formal comparisons between treatment arms. Secondary endpoints include; safety, OS, confirmed ORR, DoR, confirmed PSA_{50} response, time to pain progression, and PK.

AZD4635 plus durvalumab (Arm A) will consist of participants with mCRPC previously treated with one or more approved NHAs (e.g., abiraterone acetate, enzalutamide, apalutamide and/or darolutamide) and one or more taxanes or participants who are taxane ineligible. 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 mCRPC previously treated with docetaxel and one prior NHA (either abiraterone acetate or enzalutamide but not both; prior apalutamide is not permitted 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 PWCG3 and have ongoing androgen deprivation with serum testosterone < 50 ng/mL.

Participants will be allocated to one of the following treatment arms:

Arm A: AZD4635 ([redacted] mg PO daily) plus durvalumab (1500 mg IV 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.

or

Arm B: AZD4635 ([redacted] mg PO daily) plus durvalumab (1500 mg IV Q3W)
plus cabazitaxel (20 or 25 mg/m^2 IV Q3W as per local prescribing guidelines) (n = 80).

Participants in Arm B will receive cabazitaxel chemotherapy as per the local label. This will start approximately 1 hour (or up to a maximum of 2 hours) after the end of the durvalumab

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

Arm B participants must receive premedication to manage cabazitaxel-associated reactions (hypersensitivity or other):

- Prednisone (10 mg daily continuously [or equivalent steroid]) for the duration of cabazitaxel administration
- Primary G-CSF prophylaxis (G-CSF should be administered according to the product label and institutional standards).

An archival tumour sample is required or the participant must be willing to undergo a baseline tumour biopsy (see Section 8.6.1.3). The collection of paired tumour biopsies will be requested during the study; however, this is optional (see Section 8.6.2.1).

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

If a participant is symptomatic for active COVID-19 infection during a site visit, he may be prescribed a COVID-19 test. Dosing may continue while results are awaited, per the Investigator's discretion and local guidelines, and the Medical Monitor/AstraZeneca Study Physician should be consulted. For participants who test positive (for COVID-19) the study drugs may be temporarily interrupted and later resumed, per the Investigator's discretion and local guidelines, and this should be discussed with the Medical Monitor/AstraZeneca Study Physician. Where applicable, home or remote visits may be conducted for study assessments and study drug administration (see Appendix L).

Participants in Arm B (AZD4635 plus durvalumab and cabazitaxel) will have disease assessments/imaging at baseline and every 9 weeks (± 7 days) from the start of dosing for the first 27 weeks and then every 12 weeks (± 7 days) thereafter. A safety assessment to determine the safety and tolerability of this combination will be completed by the SRC after the first 6 participants have completed a safety assessment period of at least 1 cycle (see Section 4.1.1).

The participant reported outcome (PRO) instruments, a BPI-SF (see Appendix J) and FACT-P (see Appendix K) will be administered to all participants. These two instruments will be used

to assess pain and quality of life in study participants. These will be measured as shown in Table 1 and Table 2

The two arms will enrol participants with metastatic disease documented by either bone lesions on bone scan or with soft tissue disease that is evaluable for assessment. 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 will enroll and assign to study treatment approximately 80 participants. At least 40 participants with RECIST v1.1-measurable disease (Section 5.1) at baseline will be enrolled and assigned to study treatment in Arm B, and the remainder of participants in the arm (n = 40) may have bone-only disease or measurable disease. The primary analysis, rPFS, will be assessed, and is defined as the time from first dose to radiographic progression as determined by the Investigator per RECIST v1.1 for soft tissue disease or PCWG3 for bone disease or death from any cause, whichever occurs first. Overall survival, ORR, DoR, PSA_{50} response, and time to pain progression will also be evaluated for efficacy.

A futility interim analysis is planned for Arm B based on PSA_{50} response for approximately n = 30 dosed participants. 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.

4.1.1 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 Safety Review Committee (SRC). The SRC will evaluate all available toxicity information (including AEs and laboratory abnormalities that are not DLTs (defined in 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.

4.2 Scientific Rationale for Study Design

Better SOC treatments for prostate cancer patients who have exhausted treatments are needed. The recent and ongoing responses observed in patients with prostate cancer receiving AZD4635 monotherapy or AZD4635 and durvalumab suggest further investigation is warranted.

Arms will assess the following combination of therapies: AZD4635 plus anti-PD-L1 (durvalumab) and AZD4635 plus anti-PD-L1 (durvalumab) plus cabazitaxel. AZD4635 appears to have increased efficacy in combination with anti-PD-L1 in prostate cancer due to increased immune activation compared to single agent AZD4635 based on the results of the Phase I study of the two treatments. At the data cut-off (DCO) of 02 December 2019, 8 subjects have achieved objective response (OR) per Response Evaluation Criteria in Solid Tumours (RECIST) v1.1. Two subjects (durvalumab combination) had complete responses and 6 subjects had partial responses (monotherapy [n = 2] and durvalumab combination [n = 4]). Participants with an OR (CR+PR) have had durations of response that ranges from 2.30 to 25.82 months with several ongoing response at the DCO.

The combination of the checkpoint inhibitor pembrolizumab (anti-PD-1) and docetaxel has been investigated in the KEYNOTE 365 study where the checkpoint inhibitor was added to the SOC chemotherapy. It has been reported that pembrolizumab alone leads to a relatively low response rate of ~5% and PSA_{50} of 11% (KEYNOTE-199) (Antonarakis et al 2019). In KEYNOTE 365, an ORR of 14% (5/36) and PSA_{50} of 31% (22/71) were reported with the most notable result being a median radiographic progression-free survival (rPFS) of

8.3 months (Massard et al. 2019) which is longer than that reported with single-agent docetaxel (3.9 months [Rathkopf et al. 2018]). Additionally, the recently published CARD study (de Wit et al. 2019) demonstrated an imaging-based median PFS of ~8.2 months for the cabazitaxel arm in a post-NHA, post-docetaxel unselected mCRPC participant population.

We hypothesize that the combination of AZD4635 plus the checkpoint inhibitor (anti-PDL1) durvalumab plus cabazitaxel would lead to an increased rPFS in the post-docetaxel setting by decreasing the immunosuppressive environment and counteracting the effects of ADO which can limit the response to chemotherapy and anti-PD-1/and i-PDL1. For patients who have progressed despite therapy with taxanes and NHA or patients who will not tolerate therapy with taxanes, there are limited options. Data from the Phase I study of AZD4635 and durvalumab as presented above supports further exploration of this combination in mCRPC.

4.3 Justification for Dose

Treatment study intervention and dose for this study are defined as Arm A and Arm B:

- **Arm A:** AZD4635 ([CCI] mg PO daily) plus durvalumab (1500 mg IV 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/m^2 IV Q3W as per the local prescribing guidelines) plus prednisone 10 mg daily PO continuously for a maximum of 10 cycles plus primary G-CSF prophylaxis, after which AZD4635 will continue at [CCI] mg PO daily with durvalumab 1500 mg Q4W without cabazitaxel/prednisone (Note: a 6 participant safety run-in will precede the full Arm B enrollment of a total of n = 80).

AZD4635 ([CCI] mg PO daily) plus Durvalumab (1500 mg IV)

Data from the ongoing Phase I study of AZD4635 both as monotherapy and combination therapy with durvalumab in subjects with relapsed or refractory solid tumours has demonstrated a favourable safety profile as well as activity in prostate cancer in particular. The durvalumab dose is consistent with that used in the Phase I study of AZD4635 in combination with durvalumab and the AZD4635 dose of [CCI] mg is the recommended Phase II dose of the capsule formulation for this combination based on the data from the relative bioavailability study which was conducted to determine the exposure of the capsule formulation of AZD4635 in comparison to that seen with the nanosuspension in the Phase I study D8730C00001.

The most common AEs seen in participants include nausea, fatigue, constipation and dizziness. One participant in the Phase Ia dose-escalation cohort ([CCI] mg AZD4635 plus 1500 mg durvalumab) experienced Grade 2 DLTs of nausea and fatigue that required dose reduction of AZD4635 to [CCI] mg. The RP2D of AZD4635 both as monotherapy and

combination therapy with durvalumab was identified as CCI mg AZD4635 nanosuspension daily and 1500 mg durvalumab Q4W.

AZD4635 was initially developed as a nanosuspension, but recently a capsule formulation was developed. The capsule formulation has been evaluated for relative bioavailability in a study of healthy adult male volunteers. In this study, at doses of CCI mg of AZD4635, the capsule formulation was found to have a higher AUC_{0-48} of ~110% of the nanosuspension and C_{max} of 128% of the nanosuspension. Due to the higher C_{max} with the capsule formulation, the overlapping exposure seen with nanosuspension formulation at a CCI mg QD dose, and the desire to minimize C_{max} related AEs, the RP2D for the capsule formulation is CCI mg QD.

AZD4635 (CCI mg PO daily) plus Durvalumab (1500 mg IV) plus Cabazitaxel (20 or 25 mg/m^2 IV Q3W)

As there is no predicted drug-drug interaction (DDI) between AZD4635 and cabazitaxel or between either of these drugs and cabazitaxel, we plan to study the triplet combination of AZD4635 plus durvalumab plus cabazitaxel in Arm B at the same proposed Phase 2 dose of CCI mg AZD4635 capsule formulation. In Arm B, AZD4635 at CCI mg capsule formulation (CCI mg capsules) plus 1500 mg durvalumab (Q3W) plus 20 mg/m^2 or 25 mg/m^2 (or as per locally approved label) of cabazitaxel (Q3W) with prednisone 10 mg PO twice daily continuously will be administered. Cabazitaxel will be administered for a maximum of 10 cycles. After cycle 10 durvalumab + AZD4635 will be administered Q4W.

Durvalumab has been dosed in 3-week cycles in a number of studies when used in combination with chemotherapy. In two studies, AstraZeneca's D419SC00001 and the Canadian Clinical Trials Group (CCTG) study NCT02537418 durvalumab has been investigated ± tremelimumab. In a Phase I study of durvalumab ± tremelimumab in combination with multiple standard platinum-based chemotherapy regimens in participants with incurable advanced or metastatic cancer (NCT02357418), the dose escalation/regimens initially included a fixed dose cohort of durvalumab 1125 mg plus tremelimumab 56 mg Q3W concurrent with platinum-based doublet chemotherapy and then subsequently, a cohort of durvalumab 1500 mg plus tremelimumab 75 mg Q3W concurrent with chemotherapy. At the last reported data cut-off, 111 participants had been dosed with 7 different chemotherapy regimens. Overall, toxicities were related to the chemotherapy core regimen and appeared as expected in severity and frequency and there were no DLTs. Toxicities related to durvalumab and tremelimumab were also those expected for these agents, although a number of potential IO related toxicities such as diarrhoea, skin rash, hepatic function changes or pneumonitis were difficult to differentiate from those reported for cytotoxic agents. As expected, there were more IO related toxicities reported for dose levels containing tremelimumab. In general, all regimens were tolerable and manageable at all dose levels.

In addition, PK modelling suggested that a Q3W schedule did not impose a significant

increased safety risk based on the expected durvalumab exposures.

Study D419SC00001 evaluated durvalumab 1120 mg plus tremelimumab 75 mg Q3W given concurrently with carboplatin AUC 5 mg/mL/min and etoposide 100 mg/m^2 Q3W, followed by durvalumab 1120 mg monotherapy Q3W. There was one DLT reported in 6 patients however, the safety profile of this combination of durvalumab at 1120 mg plus tremelimumab 75 mg concurrent with platinum doublet chemotherapy using a Q3W schedule was declared tolerable and manageable.

Taken together, the totality of data supports the combination of 1500 mg durvalumab combined with chemotherapy on a q3 week schedule.

Cabazitaxel 25 mg/m^2 administered Q3W was granted FDA approval in 2010 for the treatment of patients with mCRPC previously treated with a docetaxel-containing regimen. In 2017, the FDA approved a lower dose of cabazitaxel (20 mg/m^2) Q3W in combination with prednisone for the same indication.

On 17 March 2011 the European Commission issued approval to market cabazitaxel at a recommended dose of 25 mg/m^2 administered Q3W with oral prednisolone or prednisone for hormone-refractory metastatic prostate cancer patients previously treated with a docetaxel-containing regimen. Participants on clinical trials treated with cabazitaxel experienced adverse reactions and laboratory abnormalities. Such events occurring in greater than 10% of participants were neutropenia, anaemia, leukopenia, thrombocytopenia, diarrhoea, fatigue, nausea, vomiting, constipation, asthenia, abdominal pain, haematuria, back pain and anorexia. Grade 3-4 infections were reported in 20% of participants on the 25 mg/m^2 dose arm and in 10% of participants on the 20 mg/m^2 arm. Febrile neutropenia occurred in 9% of participants on the higher dose arm and 2% on the 20 mg/m^2 arm. The most common reasons for dose discontinuation were fatigue and haematuria.

Refer to the US prescribing information or the EU SmPC for details on current prescribing information. After approximately 6 participants in the arm with AZD4635 plus durvalumab plus cabazitaxel have been enrolled and treated for at least one cycle, we will review the safety information for the AZD4635 plus durvalumab plus cabazitaxel treatment arm, as well as available PK data, particularly because the combination of AZD4635 plus durvalumab plus cabazitaxel has not been evaluated previously(see Section 4.1.1).

4.4 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 per Section 8.3. 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. SAEs will be reported to the Sponsor using a paper format. Drug accountability information must still be collected until such participants have completed treatment.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

In this protocol, 'enrolled' participants are defined as those who sign the informed consent.

5.1 Inclusion Criteria

Age

1 Participant must be 18 years of age inclusive at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2 Histologically confirmed adenocarcinoma of the prostate

- 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.

3 Known castrate-resistant disease, defined as:

- 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.

4 Evidence of disease progression ≤ 6 months defined by one or more of the following:

- 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. The first rising PSA (measure 2) should be taken at least 7 days after the reference value. A third confirmatory PSA measure is required (2^{nd} and beyond the reference level) to be greater than the second measure and it must be obtained at least 7 days after the 2^{nd} measure. If this is not the case, a fourth PSA measure is required to be taken and be greater than 2^{nd} measure. The third (or the fourth) confirmatory PSA should be taken within 4 weeks prior to study entry.

5 Must have measurable disease:

- 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).

Weight

6 Body weight > 30 kg at screening.

Reproduction

7 Willingness to adhere to the study treatment-specific contraception requirements: Participants must be surgically sterile or using an acceptable method of contraception (defined as a male condom in conjunction with spermicides) for the duration of the study (from the time they sign ICF) and for 12 weeks (3 months) after the last dose of AZD4635 and/or durvalumab and for 24 weeks (6 months) after the last dose of cabazitaxel to prevent pregnancy in a female partner. Participants must not donate or bank sperm for 24 weeks after treatment. The reporting of any pregnancy in the female partner of a participant is described in Section 8.3.9.1.

Bone Marrow Reserve and Organ Function

8 Adequate bone marrow reserve and organ function as demonstrated by all of the following laboratory values:

- Absolute neutrophil count (ANC) ≥ 1.5×10^9/L
- Platelet count ≥ 100×10^9/L
- Haemoglobin ≥ 9.0 g/dL (≥ 10.0 g/dL for Arm B)
- Creatinine ≤ 1.5 × ULN concurrent with creatinine clearance ≥ 40 mL/min (measured or calculated by Cockcroft and Gault equation); confirmation of creatinine clearance is only required when creatinine is > 1.5 × ULN.

Additional Inclusion Criteria Specific for Arm A

Note: 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).

9 Adequate organ function for Arm A as demonstrated by all of the following laboratory values:

- Alanine aminotransferase (ALT) ≤ 2.5 × the upper limit of normal (ULN) if no demonstrable liver metastases or ≤ 5 × ULN in the presence of liver metastases.

- Aspartate aminotransferase (AST) ≤ 2.5 × ULN if no demonstrable liver metastases or ≤ 5 × ULN in the presence of liver metastases
- Total bilirubin (TBL) ≤ 1.5 × ULN
- TBL ≤ 2.0 × ULN in the case of known Gilbert syndrome with normal direct bilirubin

10 Participants in Arm A must have received the following prior therapy:

- Maximum of 3 lines of therapy in the mCRPC setting
- Prior therapy with one or more NHAs (e.g., abiraterone acetate, enzalutamide, apalutamide, darolutamide) in either hormone-sensitive or hormone-refractory settings
- Prior therapy with one or more lines of taxanes (e.g., docetaxel and/or cabazitaxel)
- Alternatively, must be taxane-ineligible
- Prior therapy can be in either the hormone-sensitive or the hormone-refractory setting
- Participants who were eligible for both Arm A and Arm B will be preferentially allocated to Arm B, until enrollment of Arm B is completed.

Additional Inclusion Criteria Specific for Arm B

11 Adequate organ function for Arm B as demonstrated by all of the following laboratory values:

- AST and/or ALT ≤ 1.5 × ULN
- TBL ≤ ULN
- TBL ≤ 2.0 × ULN in the case of known Gilbert syndrome with normal direct bilirubin

12 Participants in Arm B must have received the following prior therapy:

- 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 (e.g., 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 inclusion criteria for Arm B will be allocated preferentially to that arm until recruitment to that arm is completed.

Other Inclusion Criteria

13 World Health Organisation (WHO) performance status of 0-1 with no clinical deterioration over the previous 2 weeks prior to the 28-day screening period and likely able to complete at least 12 weeks of treatment.

14 Normotensive or well controlled blood pressure (BP) (systolic < 150 and diastolic < 90), with or without current antihypertensive treatment. If there is a diagnosis or history of hypertension, participant must have adequately controlled BP on antihypertensive medications.

15 Availability of an archival tumour sample. If an archival tumour sample is not available, then a tumour biopsy will be required to obtain a tumour sample.

16 Participants must be able to swallow and retain oral medications (e.g., AZD4635 and/or prednisone).

Informed Consent

17 Capable of giving signed informed consent as described in Appendix A and able to comply with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

18 Provision of signed and dated written Optional Genetic Research Information informed consent prior to collection of samples for optional genetic research that supports Genomic Initiative.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1 Active brain metastases or leptomeningeal metastases. Participants with brain metastases are eligible if treated and there is no evidence of progression for at least 8 weeks after treatment is completed and within 28 days prior to the first dose of study intervention.

2 There must be no requirement for immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone/equivalent) for at least 2 weeks prior to study enrollment. For current or prior use of immunosuppressive medication within 14 days before the first dose the following will be exceptions to this:

- Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra-articular injection)
- Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent
- Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication)

3 Participant with a history of pneumonitis.

4 History of a second malignancy that is progressing and/or received active treatment ≤ 3 years before the first dose of study intervention.

5 As judged by the Investigator, any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension, active bleeding diatheses, active infection including hepatitis B, hepatitis C, and human immunodeficiency virus, chronic gastrointestinal diseases (e.g., Crohn's disease, chronic colitis), symptomatic congestive heart failure, unstable angina pectoris, uncontrolled cardiac arrhythmia, or active interstitial lung disease (ILD). Screening for chronic conditions is not required.

6 Creatinine clearance < 40 mL/min (calculated by Cockcroft-Gault equation).

7 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.

8 History of allogeneic organ transplantation.

9 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

10 History of active primary immunodeficiency.

11 Active **tuberculosis** infection (clinical evaluation that may include clinical history, physical examination and radiographic findings, and tuberculosis testing in line with local practice).

12 Receipt of live attenuated vaccine within 30 days prior to the first dose of study intervention.

Additional Exclusion Criteria Specific for Arm B: Medical Conditions

13 Participant with active grade ≥ 2 peripheral neuropathy

14 Participant with active grade ≥ 2 stomatitis

Prior/Concomitant Therapy

15 Any small-molecule, biologic, or hormonal agent from a previous treatment regimen or clinical study within 21 days or 5 half-lives (whichever is shorter) prior to the first dose of

study intervention. At least 7 days must have elapsed between the last dose of such agent and the first dose of study intervention. Exception: androgen-deprivation therapy is permitted.

16 History of hypersensitivity to any of the study drugs or any of the study drug excipients including hypersensitivity to polysorbate-80 if allocated to cabazitaxel.

17 Nitrosourea or mitomycin C within 6 weeks of the first dose of study intervention.

18 Prescription or non-prescription drugs or other products known to be sensitive BCRP, OATP1B1/3, OAT1, OCT1, OCT2, MATE1 and P-gp substrates or to be strong inhibitors/inducers of CYP1A2 (see Appendix I), which cannot be discontinued 2 weeks prior to Day 1 of dosing and withheld throughout the study, until 2 weeks after the last dose of study intervention.

19 **Exclusion Criteria for Arm B:** Concurrent or planned treatment with strong inhibitors or strong inducers of cytochrome P450 3A4/5 (CYP3A4/5) are excluded (a 2-week washout period is required for participants already on these treatments) (see Appendix I).

20 Herbal preparations/medications are not allowed throughout the study. These herbal medications include but are not limited to St. John's wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone, yohimbe, saw palmetto, and ginseng. Participants should stop using these herbal medications 7 days prior to the first dose of study intervention. Exceptions may be agreed, but the circumstances must be reviewed by the Medical Monitor/AstraZeneca Study Physician in advance.

21 Ongoing treatment with warfarin (Coumadin).

22 Major surgery (excluding placement of vascular access) within 4 weeks of the first dose of study intervention.

23 Radiotherapy with a wide field of radiation within 4 weeks or radiotherapy with a limited field of radiation for palliation within 2 weeks of the first dose of study intervention.

Prior/Concurrent Clinical Study Experience

24 AZD4635 in the present study (i.e., dosing with AZD4635 previously initiated in a different arm in this study) or prior therapy with AZD4635 or any other $A_{2A}R$ antagonist or other CD73/CD39 antagonists.

25 History of allogeneic organ, or other transplant, such as bone marrow transplant.

26 With the exception of alopecia, any unresolved toxicities from prior therapy greater than Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 Grade 1 at the time of starting study treatment. Participant with chronic Grade 2 unresolved toxicities may be eligible following discussion with the Medical Monitor/AstraZeneca Study Physician.

27 Concurrent enrollment into another therapeutic clinical trial.

28 Concomitant treatment with another adenosine 1 receptor (A_1R) antagonist that would increase risk of seizure (e.g., theophylline, aminophylline).

Diagnostic Assessments

29 Any of the following cardiac criteria:

- Mean resting corrected QT interval (QTcF) > 470 msec obtained from 3 ECGs
- Any clinically important abnormalities in rhythm, conduction, or morphology of resting ECGs, e.g., complete left bundle branch block, third-degree heart block
- Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalaemia, congenital long QT syndrome, or family history of long QT syndrome or unexplained sudden death under 40 years-of-age
- Left ventricular ejection fraction < 55% or the lower limit of normal of the institutional standard, ascertained by an echocardiogram or multiple-gated acquisition (MUGA) that has been obtained in the 6 months prior to screening. If there has been a change in the participant's cardiac status, or if there has not be an echocardiogram or MUGA within the 6 months prior to study enrollment, this should be performed as part of the screening assessments.

Other Exclusions

30 Judgment by the Investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions and requirements.

5.3 Lifestyle Considerations

No restrictions are required.

5.3.1 Meals and Dietary Restrictions

Participants in Arm B must refrain from consumption of Seville oranges, grapefruit or grapefruit juice, pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices from 7 days before the first dose of study intervention until after the final dose.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently assigned to a study intervention/entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Participants defined as screen failures may be rescreened under certain circumstances. Consideration will be given, for example, to the following:

- Participants with out-of-range laboratory values will be allowed to repeat the relevant laboratory safety assessments within the screening period, unless the laboratory values are reflective of an established medical condition and are unlikely to improve during the screening period.
- Participants for whom screening procedures are not completed within the 28-day window.
- Participants taking a prohibited medication can be considered for the study after the appropriate washout period. This is only applicable in instances where the withdrawal of the medication is clinically appropriate and unlikely to adversely affect the condition for which the medication has been prescribed.

Other conditions may be discussed with the Medical Monitor/AstraZeneca Study Physician.

Rescreening should be documented so that its effect on study results, if any, can be assessed. All rescreened requests need to be discussed by the Medical Monitor/AstraZeneca Study Physician.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened participants should be assigned the same participant number as for the initial screening.

6 STUDY INTERVENTION

Study interventions is defined as any IP(s) (including marketed comparator) intended to be administered to a study participant according to the study protocol. Study intervention in this study refers to AZD4635, durvalumab and cabazitaxel. In this protocol AZD4635, durvalumab and cabazitaxel are also referred to as either study drugs, study interventions, IPs, or investigational medicinal products – and these terms are used interchangeably.

On days when multiple IPs are given together, it is advised that AZD4635 is given first followed by durvalumab and then cabazitaxel.

6.1 Investigational Products

Table 4 Investigational Products

ARM Name	A and B	A and B	B only
Intervention Name	**AZD4635**	**Durvalumab**	**Cabazitaxel**
Type	Small Molecule	Biologic	Chemotherapy
Dose Formulation	capsules	vial	vial
Unit Dose Strength(s)	CCI mg or CCI mg	500 mg vial solution for infusion after dilution, 50 mg/mL	60 mg/1.5 mL supplied with diluent (5.7 mL)
Dosage Level(s)	CCI mg PO daily (Arm A and Arm B)	1500 mg IV Q4W (Arm A) 1500 mg IV Q3W (Arm B)	20 or 25 mg/m^2 IV Q3W as per the local label (Arm B only)
Route of Administration	Oral	Intravenous	Intravenous
Use	Intervention	Intervention	Intervention
IMP and NIMP	IMP	IMP	IMP
Sourcing	AstraZeneca	AstraZeneca	Commercially sourced
Packaging and Labelling	Study intervention will be provided in high-density polyethylene (HDPE) bottles induction-sealed with desiccant. Each bottle will be labelled in accordance with Good Manufacturing Practice	Durvalumab will be provided as a solution in clear glass vials. Each vial will be labelled in accordance with GMP Annex 13 and/or per country regulatory requirement.	Commercially sourced study intervention will be provided.

	(GMP) Annex 13 and/or per country regulatory requirements.		
Current/Former Name(s)	-	-	JEVTANA®

6.2 Preparation/Handling/Storage/Accountability of Interventions

The Investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all study intervention received and that any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive the study intervention and only authorised site staff may supply or administer the study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the Investigator and authorised site staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

6.2.1 AZD4635

AZD4635 [redacted] mg PO will be administered on a continuous schedule in Arms A and B unless safety findings indicate that a change is required.

No routine prophylactic anti-emetic treatment is required at the start of study treatment; however, participants should receive appropriate anti-emetic treatment at the first onset of nausea or vomiting. If a participant has a known history of nausea and vomiting with prior therapy, consider the use of prophylactic anti-emetics. They should continue as required thereafter, in accordance with local treatment practice guidelines. Alternatively, AZD4635 capsules can be taken with food.

This IP will be supplied by AstraZeneca. AZD4635 will be dispensed to participants weekly or prior to beginning a new cycle during scheduled visits to the clinic or by delivery. The batch number of the study drug dispensed to the participant should be entered on the eCRF, if applicable.

As per international guidance on anti-emetic use in cancer subjects (ESMO, NCCN),

generally a single agent anti-emetic should be considered (e.g., dopamine receptor antagonist, antihistamines or dexamethasone).

Dosing and handling instructions and participant emergency contact details will be provided to participants in writing.

Whenever possible, all doses of AZD4635 should be taken at approximately the same times each day, with or without food. The capsule formulation should not be crushed, chewed, or dissolved when taken orally. If vomiting occurs after AZD4635 dosing, the participant should not re-dose, and the participant should take the allotted dose at the next scheduled time.

Should a participant miss a scheduled dose, the participant will be allowed to take the dose up to a maximum of 4 hours after the scheduled dose time. If greater than 4 hours after the scheduled dose time have elapsed, the missed dose should not be taken, and the participant should take the allotted dose at the next scheduled time. If a participant needs to take the dose earlier for any reason, the participant can take the dose up to 4 hours earlier than the scheduled dose time. The participant should make every reasonable effort to take the study intervention on time. A dosing diary will be provided to the participant to record the date and time dose(s) were taken. A copy of the dosing diary is provided in the study reference materials (see Section 6.4.

Additional information about the IP may be found in the IB.

Each bottle will be labelled as described in Table 4.

6.2.2 Durvalumab

Durvalumab 1500 mg will be administered via IV once every 4 weeks in Arm A. In Arm B durvalumab 1500 mg IV will be administered once Q3W for first 10 cycles and then Q4W thereafter.

Durvalumab will be supplied by AstraZeneca as a 500-mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine hydrochloride, 275 mM trehalose dihydrate, and 0.02% (weight/volume [w/v]) polysorbate 80; it has a pH of 6.0 and density of 1.054 g/mL. The nominal fill volume is 10 mL. IP vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Drug product should be kept in original packaging until use to prevent prolonged light exposure.

Durvalumab will be labelled as described in Table 4.

Additional information about the IP may be found in the durvalumab IB.

6.2.2.1 Preparation of Durvalumab Dose for Administration with an IV Bag

The dose of durvalumab for administration must be prepared by the Investigator's or the site's designated Investigational Product Manager using an aseptic technique.

Total time from needle puncture of the durvalumab vial to the start of administration should not exceed:

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

A dose of 1500 mg will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab concentration ranging from 1 to 20 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm filter. Add 30.0 mL of durvalumab (i.e., 1500 mg of durvalumab) to the IV bag. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

Standard infusion time is one hour; however, if there are interruptions during infusion, the total allowed infusion time should not exceed 8 hours at room temperature.

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

The IV line will be flushed with a volume of IV diluent equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered; alternatively, complete the infusion according to institutional policy to ensure the full dose is administered.

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

6.2.3 Cabazitaxel

Participants allocated to Arm B will receive cabazitaxel 20 mg/m^2 or 25 mg/m^2 as a 1-hour IV infusion (as per local label) on Day 1 of each cycle Q3W for the first 10 cycles according to institutional standards of care. Cabazitaxel will be locally sourced from a commercial supplier.

The participant should be pre-medicated with prednisone 10 mg PO continuously.

Pre-medicate with the following intravenous medications at least 30 minutes prior to each dose of cabazitaxel to reduce the risk and/or severity of hypersensitivity:

- antihistamine (dexchlorpheniramine 5 mg or diphenhydramine 25 mg or equivalent antihistamine),
- corticosteroid (dexamethasone 8 mg or equivalent), and

- H2 antagonist (ranitidine 50 mg or equivalent H_2 antagonist)

For countries where IV antihistamines are not available, oral antihistamines can be used according to local practice.

Prophylactic antiemetic therapy should be administered according to local institutional practices and standards.

Primary prophylactic G-CSF is required at the beginning of each new cycle for all participants in the cabazitaxel arm. G-CSF should be administered according to the product label and institutional standards.

6.2.3.1 Preparation of Cabazitaxel Dose for Administration with an IV Bag

Cabazitaxel (JEVTANA) is a sterile, non-pyrogenic, clear yellow to brownish-yellow viscous solution and is available in single-dose vials containing 60 mg cabazitaxel (anhydrous and solvent free) and 1.56 g polysorbate 80.

Each mL contains 40 mg cabazitaxel (anhydrous) and 1.04 g polysorbate 80.

The DILUENT for JEVTANA is a clear, colourless, sterile, and non-pyrogenic solution containing 13% (w/w) ethanol in water for injection, approximately 5.7 mL.

JEVTANA requires **two** dilutions prior to intravenous infusion. JEVTANA should be diluted only with the supplied DILUENT for JEVTANA, followed by dilution in either 0.9% sodium chloride solution or 5% dextrose solution.

Do not use PVC infusion containers or polyurethane infusion sets for preparation and administration of JEVTANA infusion solution. JEVTANA should not be mixed with any other drugs.

For preparation and administration instructions for cabazitaxel, refer to the respective product labels, either the US prescribing information or the EU SmPC.

6.3 Measures to Minimise Bias: Methods for Assigning Treatment Groups

Treatment arm will be selected by the Investigator based on the inclusion/exclusion criteria (Section 4.4) and the open arm(s) (as of November 2020, the Sponsor stopped enrolment in Arm A following decisions at the program level, not related to any safety issues).

An IWRS will be used to assign potential participant a unique enrollment number (7-digit e-code). All participants will be stratified by the presence of measurable soft tissue metastasis (per RECIST v1.1) or bone-only metastasis (per PCWG3 criteria) to ensure there is sufficient

number of participants in each stratum in Arm B as specified in the Section 4.1.

Investigator(s) should keep a record, the participant screening log, of participants who entered pre-study screening.

The Investigator(s) will:

- Obtain a signed informed consent from the potential participant before any study-specific procedures are performed.
- Assign potential participant a unique enrollment number (i.e., E-code) using IWRS. The E-code is sequentially issued and will be used to identify the participant on all study-related documents including the eCRF.
- Determine participant eligibility. See Sections 5.1 and 5.2.
- Declare if participant has soft tissue disease measurable by RECIST v1.1 or bone-only disease measurable by PCWG3 using the IWRS.
- Declare if: participant received therapy with one NHA in the setting of mCRPC and docetaxel in the setting of mCRPC setting with a maximum of 3 lines of therapy (Arm A)
  OR
  participant received prior therapy with one NHA in the metastatic setting and no prior taxane for treatment of mCRPC (Arm B).
- Allocate eligible participant to the appropriate treatment arm and stratum, if they are open.

Allocation will be done centrally via IWRS after participant eligibility is established and prior to treatment. Every effort should be made to minimise the time between allocation and starting study treatment. It is recommended that participants commence study treatment as soon as possible after allocation.

If the participant is found to be ineligible during screening, the participant must be screen failed in the IWRS.

Specific directions concerning the use of the IWRS will be provided in a separate instruction manual. If a participant withdraws from participation in the study, then his assigned codes cannot be reused.

6.4 Study Intervention Compliance

When participants are dosed at the site, they will receive the study intervention directly from the Investigator or designee, under medical supervision. The date, and time if applicable, of dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the

study intervention.

When participants self-administer study intervention (AZD4635) at home the participant will be required to complete a dosing diary. Dosing compliance will be reviewed with the participant at the beginning of a new treatment cycle. The site staff will count and document the amount of study drug taken and returned by the participant. If a dose is missed, the reason must be noted in the diary.

Compliance will be assessed by direct questioning, counting returned capsules, etc., during the site visits and documented in the source documents and eCRF. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

Participants should return all unused AZD4635 and empty containers. The Investigator or pharmacy must retain records of all study drugs administered.

A record of the number of study intervention capsules dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions, will also be recorded in the eCRF.

6.5 Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration, including start and end dates
- Dosage information including dose and frequency

The Medical Monitor/AstraZeneca Study Physician should be contacted if there are any questions regarding concomitant or prior therapy.

Participants must abstain from taking prescription or non-prescription drugs (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of the study intervention until completion of the follow-up visit unless, in the opinion of the Investigator and sponsor, the medication will not interfere with the study.

Paracetamol/Acetaminophen, at doses of ≤ 2 grams/day, is permitted for use any time during the study. Other concomitant medications may be considered on a case-by-case basis by the Investigator in consultation with the Medical Monitor/AstraZeneca Study Physician.

6.5.1 Permitted Concomitant Medications

The following concomitant medications will be permitted:

- Medical castration therapy with GRH analogues may continue during this study
- Erythropoietin at the time of screening for the study may continue, provided the participant had been taking it for more than one month at the time study treatment is started
- Treatment with bisphosphonates or denosumab for the treatment of bone metastases
- Treatment with megestrol acetate when prescribed for appetite stimulation
- Low molecular weight heparin. It is recommended that participants treated with an anticoagulant should have their anticoagulation monitored carefully and dose adjusted accordingly. Warfarin (Coumadin) is not permitted.
- Hormones for non-cancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy).

During the cabazitaxel study intervention, participants should receive concomitant prophylactic medications and the recommended anti-emetic therapy shown below.

  - Prednisone (10 mg daily continuously [or equivalent steroid]) for the duration of cabazitaxel administration
  - Primary G-CSF prophylaxis

Administered intravenously 30 minutes before cabazitaxel:

  - Antihistamine (dexchlorpheniramine 5 mg, diphenhydramine 25 mg, or equivalent antihistamine)
  - Corticosteroid (dexamethasone 8 mg or equivalent)
  - H_2 antagonist (ranitidine 50 mg or equivalent H_2 antagonist
  - Antiemetic prophylaxis (oral or intravenous) as needed.

6.5.2 Prohibited or Restricted Medications

The following interventions listed are restricted or prohibited and are to be used with caution or not at all as described. Details on disallowed medications are included in Appendix I.

Table 5 Prohibited Medications with AZD4635

Restricted medication/class of drug:	Additional Information
CYP1A2 inhibitors or inducers (Table 24).	Contribution of CYP1A2 to AZD4635 metabolism appears to be approximately 80%. Potent inhibitors or inducers of CYP1A2 should be avoided during administration of AZD4635. Refer to Appendix I for a list of the prohibited medications.

Table 6 Prohibited Medications with AZD4635

Prohibited medication/class of drug:	Additional Information
No other investigational therapy should be given to participants. No anticancer agents other than the study medications should be given to participants.	If such agents are required for a participant, then the participant must first be withdrawn from the study.
Since AZD4635 is an *in vitro* inhibitor of BCRP (IC_{50} 6.2 µM) and OAT1 (IC_{50} 6.6 µM), there is a risk of drug-drug interactions (DDIs) with sensitive substrates of BCRP (both in the gut and systemically) and OAT1 (systemically). Modelling has predicted a substantial increase in the exposure (>2 fold) of certain statins (simvastatin, rosuvastatin, and atorvastatin) when co-administered with AZD4635. The use of sensitive substrates of OATP1B1/3, OCT1, OCT2, MATE1 and P-gp is also prohibited in this study, pending results from ongoing DDI studies.	Use of potent inhibitors or inducers of BCRP and sensitive substrates of OATP1B1/3, OAT1, OCT1, OCT2, MATE1 and P-gp are prohibited throughout the study period (see Appendix I).
Herbal preparations/medications are not allowed throughout the study. These herbal medications include but are not limited to St. John's wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng.	Participants should stop using these herbal medications 7 days prior to first dose of AZD4635. Exceptions may be agreed, but the circumstances must be reviewed by the Medical Monitor/AstraZeneca Study Physician in advance.

Table 7 Prohibited Medications with Durvalumab

Prohibited medication/class of drug:	Additional information
mAbs against CTLA-4, PD-1, or PD-L1 other than those under investigation in this study	Should not be given concomitantly while the participant is on study intervention
Live attenuated vaccines	Should not be given through 30 days after the last dose of durvalumab

Prohibited medication/class of drug:	Additional information
Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumour necrosis factor-α blockers	Should not be given concomitantly, or used for premedication prior to the I-O infusions. The following are allowed exceptions: Use of immunosuppressive medications for the management of IP-related AEs Use in participants with contrast allergies. In addition, use of inhaled, topical, and intranasal corticosteroids is permitted. A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of non-immunotherapy related events experienced by the participant (e.g., chronic obstructive pulmonary disease, radiation, nausea, etc.).
Epithelial growth factor receptor tyrosine kinase inhibitors (EGFR TKIs)	Should not be given concomitantly. Should be used with caution in the 90 days post-last dose of durvalumab. Increased incidences of pneumonitis (with third generation EGFR TKIs) and increased incidence of transaminase increases (with first-generation EGFR TKIs) has been reported when durvalumab has been given concomitantly.

Table 8 Prohibited Medications with Cabazitaxel

Medication/class of drug:	Additional information
CYP3A inhibitors	Cabazitaxel is primarily metabolised through CYP3A. Strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, squinavir, telithromycin, voriconazole) may increase plasma concentrations of cabazitaxel. Avoid strong CYP3A inhibitors.
CYP3A inducers	Cabazitaxel is primarily metabolised through CYP3A. Strong CYP3A inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital) are expected to decrease cabazitaxel concentrations. Avoid strong CYP3A inducers. In addition, participants should also refrain from taking St. John's Wort.
Live attenuated vaccines	Should not be given through 3 months after the last dose of cabazitaxel.

6.5.3 Drug-Drug Interactions

Durvalumab

There is no information to date on DDIs with durvalumab either pre-clinically or in participants. As durvalumab is a monoclonal antibody and, therefore, a protein, it will be

degraded to small peptides and amino acids and will be eliminated by renal and reticuloendothelial clearance. It is therefore not expected that durvalumab will induce or inhibit the major drug metabolizing cytochrome P450 pathways. As a result, there are no expected pharmacokinetic drug-drug interactions. The mechanism of action of durvalumab involves binding to PD-L1, therefore, significant pharmacodynamic drug interactions with the commonly administered concomitant medications are not expected. Despite this, appropriate clinical monitoring in all of the planned clinical studies will be conducted to evaluate any potential DDIs.

Refer to the durvalumab IB.

AZD4635

Two independent *in vitro* studies using human liver microsomes and specific CYP inhibitors suggest that the main enzyme involved in the metabolism of AZD4635 is CYP450 1A2.Clinical drug interactions with strong inhibitors or inducers of CYP1A2 cannot be ruled out.

Therefore, use of moderate and strong inhibitors/inducers of CYP1A2 are not permitted with AZD4635. As no inhibition of CYP3A4 was observed at up to 100 μM, CYP3A4 interactions with sensitive CYP3A4 substrates at the level of the gut are considered unlikely. The risk has been further evaluated using a preliminary PBPK model developed based on in vitro data and clinical data from the on-going Phase I study. The potential for a drug interaction with midazolam (sensitive CYP3A substrate) was evaluated indicated suggested a minimal impact on midazolam exposure (AUC ratio, < 1.15) with Ki CYP3A4 of AZD4635 from 10 – 300 μM AZD4635 is an in vitro inhibitor of BCRP, OATP1A2, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, and MATE1, with respective IC50 values of 6.2, 2.3, 62, 84, 6.6, 26, 8.4, 16, and 16 μM. Based on current guidance from the FDA and EMA (FDA Guidance for Industry 2020; EMA Guideline 2012), and the predicted exposures of AZD4635, there is a potential risk of DDIs with sensitive substrates of BCRP (both in the gut and systemically). In addition, based on EMA guidance (EMA Guideline 2012), there is also potentially a risk of DDIs with sensitive substrates of OATP1B1/3, OAT1, OCT1, OCT2, and MATE1. Although an IC50 could not be calculated up to 100 μM AZD4635, P-gp interactions with sensitive P-gp substrates at the level of the gut cannot be ruled out. Therefore, use of sensitive substrates of these transporters are prohibited. Herbal preparations/medications are not allowed in studies D8730C00001, D8730C00002, and D6070C00004. These herbal medications include, but are not limited to: St. John’s wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Participants should stop using these herbal medications 7 days prior to first dose of AZD4635.

Refer to the AZD4635 IB.

Cabazitaxel

Cabazitaxel is primarily metabolised through CYP3A. Though no formal drug interaction trials have been conducted for cabazitaxel, concomitant administration of strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) is expected to increase concentrations of cabazitaxel. Therefore, coadministration with strong CYP3A inhibitors should be avoided. Caution should be exercised with concomitant use of moderate CYP3A inhibitors.

Though no formal drug interaction trials have been conducted for JEVTANA, the concomitant administration of strong CYP3A inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital) is expected to decrease cabazitaxel concentrations. Therefore, co-administration with strong CYP3A inducers should be avoided. In addition, participants should also refrain from taking St. John's Wort.

Refer to the SmPC/USPI for additional information.

6.5.4 Rescue Medication

As a result of immune-mediated AEs (imAEs) that could potentially be experienced by participants on durvalumab, steroids and other immunosuppressant rescue medication have to be made available to this participant population. The 2 products that fall into the category of immunosuppressants are infliximab (e.g., for colitis) and mycophenolate (e.g., for hepatitis). AstraZeneca supply chain will be responsible for sourcing these 2 rescue medications to the sites if local regulations prevent the use of infliximab and mycophenolate in this indication, because they are considered off-label for management of immunotherapy related toxicities. These rescue medications must be receipted, controlled, and administered by the pharmacist and stored according to the labelled storage conditions, with temperature excursions reported accordingly by the pharmacist.

There is currently no known antidote to AZD4635 and the provided treatment should be supportive care for the underlying symptoms.

There is no known antidote to cabazitaxel. The anticipated complications of overdose would consist of exacerbation of adverse reactions such as bone marrow suppression and gastrointestinal disorders. In case of overdose, the participant should be kept in a specialized unit and closely monitored. Participants should receive therapeutic G-CSF as soon as possible after the discovery of an overdose. Other appropriate symptomatic measures should be taken.

6.5.5 Other Concomitant Medications

Other medication other than that described above, which is considered necessary for the participant's safety and wellbeing, may be given at the discretion of the Investigator and

recorded in the appropriate sections of the Case Report Form (CRF).

6.6 Cabazitaxel Safety Assessment Arm B

6.6.1 Definition of Dose-Limiting Toxicity for Arm B

In Arm B, dose-limiting toxicity (DLT) criteria will be used to assess safety for Arm B in the first 6 evaluable participants. Grading of DLTs will be according to the CTCAE, Version 5.0.

A DLT is defined as an AE or abnormal laboratory value that occurs from the first dose of AZD4635 plus durvalumab plus cabazitaxel up to and including Day 21, Cycle 1 (the DLT period) that is assessed as unrelated to disease progression, intercurrent illness, or concomitant medications and that, despite optimal therapeutic intervention, meets any of the following criteria:

- Haematological toxicities CTCAE ≥ Grade 3 not attributed to cabazitaxel alone, except for neutropenia, which is addressed as:

  Neutropenia ≥ CTCAE Grade 4 or febrile neutropenia present for more than 7 days. For AZD4635/cabazitaxel/durvalumab it will not be considered a DLT if attributed to cabazitaxel only.

Non-haematological toxicity CTCAE ≥ Grade 3 including:

- QTc (Fridericia's correction) interval >500 msec or QTc increase >60 msec from baseline on 2 ECGs at least 30 minutes apart that cannot be attributed to another cause
- Convulsions, seizures, or stroke
- Nausea, vomiting, or diarrhoea that does not resolve to ≤ Grade 1 within 7 days of maximal supporting care
- Liver transaminase elevation ≥5 × but ≤8 × ULN that does not downgrade to Grade 2 within 5 days after onset with optimal medical management, including systemic corticosteroids. Transaminase elevation >8 × ULN or total bilirubin >5 × ULN will be considered a DLT regardless of duration. Any increase in AST or ALT >3 × ULN and concurrent increase in total bilirubin >2 × ULN (Hy's Law without evidence of cholestasis or alternative explanations [e.g., viral hepatitis, disease progression in the liver]).
- Any other toxicity that is ≥ CTCAE Grade 3 is clinically significant and/or unacceptable, does not respond to supportive care, results in a disruption of dosing schedule of more than 21 days, or is judged to be a DLT the Investigator in collaboration with the AstraZeneca Study Physician, Global Safety Physician, or by the SRC (see Section 4.1.1).

A DLT excludes:

- Alopecia of any grade

- Lymphopenia of any grade
- Isolated laboratory changes of any grade without clinical sequelae or clinical significance.

An evaluable participant is defined as a participant who has received AZD4635 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.

Non-evaluable participants may be replaced.

Any participant started on treatment in error because he failed to comply with all of the selection criteria but meets the criteria of an evaluable participant, will be reviewed on a case-by-case by the SRC to determine if the participant should be included or excluded in the decision with regard to recruitment to Arm B.

6.7 Dose Modification

AZD4635 and durvalumab will be administered in 4-week cycles during Arm A and in 3-week cycles during Arm B. In Arm B, cycles will increase to 4 weeks after the participant has completed ten 3-week cycles. AZD4635 dose reductions or holds and initiation of supportive care are allowed as clinically indicated by the Principal Investigator. The dose for AZD4635 is CCI mg PO QD in combination with durvalumab. Dose reductions for AZD4635 will occur in CCI mg increments. Up to 2 dose reductions of AZD4635 for toxicity will be allowed (see Table 9). All hematologic and non-hematologic toxicities will be graded according to the CTCAE, Version 5.0 criteria.

The dose for cabazitaxel is 25 mg/m^2 or 20 mg/m^2 per locally approved label. This dose can be reduced for cabazitaxel when necessary as described in following sections. The dose, which has been reduced for toxicity, must not be re-escalated. If the starting dose cabazitaxel is 25 mg/m^2, up to a maximum of 2 dose reductions will be allowed per participant. If a third dose reduction is required per the modifications (see Table 10), the participant should discontinue study treatment. If the starting dose cabazitaxel is 20 mg/m^2, up to a maximum of 1 dose reduction will be allowed per participant. If a second dose reduction is required per the modifications (Table 10), the participant should discontinue study treatment.

If a participant experiences a clinically significant and/or unacceptable toxicity not attributable to the disease or disease-related processes under investigation, dosing will be interrupted, or the dose will be reduced and supportive therapy will be administered, as required. If the toxicity does not resolve to ≤ CTCAE Grade 2 after 2 weeks of treatment, then the participant should be withdrawn from the study and observed until resolution of the toxicity unless

approved by the Medical Monitor/AstraZeneca Study Physician. Any decision to withdraw a participant from the study must be discussed with the Medical Monitor/AstraZeneca Study Physician. Maximum drug holiday allowed is 3 weeks for non-immune-mediated toxicity unless agreed with the Medical Monitor/AstraZeneca Study Physician. For immune-mediated toxicity, a longer drug holiday is permitted to allow for adequate steroid taper and should be discussed with the Medical Monitor/AstraZeneca Study Physician.

Dose delays for durvalumab are addressed in the Dosing Modification and Toxicity Management Guidelines (TMGs). However, **dose reduction for durvalumab is not permitted in Arm A or Arm B**.

Participants that discontinue one study drug may remain on the study and receive the other study drug(s) as long as they are continuing to derive clinical benefit.

Table 9 AZD4635 Dose Levels for Dose Reductions due to Toxicities

Dose Level	AZD4635[a]
-1	CCI mg PO QD
-2	CCI mg PO QD

[a] Two dose reductions are allowed for AZD4635.

Table 10 Cabazitaxel Dose Levels for Dose Reductions due to Toxicities

Dose Level	Cabazitaxel[a]	Cabazitaxel[a]
0	25 mg/m^2	20 mg/m^2
-1	20 mg/m^2	15 mg/m^2
-2	15 mg/m^2	NA

[a] Starting dose as per locally approved label for cabazitaxel.

6.7.1 Management of Toxicities Related to AZD4635 Therapy

AZD4635 dose reduction and discontinuation guidelines for non-haematologic toxicities are shown in Table 11.

Table 11 AZD4635 Dose Modifications and Discontinuation Criteria for Non-Haematologic Toxicities

CTCAE, Version 5.0 Toxicity Grade	Action
Grade 1 or 2	None required
Grade 3 or 4 and/or clinically significant[a]	Hold AZD4635
Toxicity resolved to Grade 1, Grade 2, or baseline < 14 days	Restart AZD4635 at 1 dose level reduction
Toxicity remains Grade 3 to 4 or is clinically significant[a] >14 days	Discontinue AZD4635

CTCAE, Version 5.0 Toxicity Grade	Action
Recurrence of Grade 3	Reduce one more dose level if available (see Table 9) or if not discontinue AZD4635
Recurrence of Grade 3 cardiac event[a]	Discontinue AZD4635
Recurrence of Grade 4	Discontinue AZD4635

[a] Includes significant change in CK/CK-mb ratio (relative index > 5%), increase in heart rate of + 25 bpm (up to 100 to 125 bpm) for more than 24 hours or increase in heart rate > 125 bpm for more than 12 hours, and QTc prolongation > 500 ms.

6.7.2 Management of Toxicities Related to Durvalumab Therapy

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

- Treat each of the toxicities with maximum supportive care (including holding the agent suspected of causing the toxicity if required).
- If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same assigned dose of durvalumab along with appropriate continuing appropriate supportive care.
- All toxicities will be graded according to CTCAE, Version 5.0.

6.7.2.1 Specific Toxicity Management Guidelines and Dose Modification Information for Durvalumab

Comprehensive TMGs have been developed to assist investigators with the recognition and management of toxicities associated with use of the immune-checkpoint inhibitor durvalumab [MED4736] (PD-L1 inhibitor). These TMGs are applicable to the management of participants receiving durvalumab as monotherapy. Additionally, these guidelines are applicable when durvalumab is used alone or, when other anti-cancer drugs (i.e., antineoplastic chemotherapy, targeted agents) are administered concurrently or sequentially with durvalumab as part of a protocol-specific treatment regimen. The TMGs provide information for the management of immune mediated reactions, infusion-related reactions, and non-immune-mediated reactions that may be observed with checkpoint inhibitor monotherapy or combination checkpoint inhibitor regimens, with specific instructions for checkpoint inhibitor-specific dose modifications (including discontinuation) and treatment interventions. Investigators are advised however to use local practice guidelines and consult local references for the management of toxicities observed with other anti-cancer treatment.

The most current version of the TMGs is provided to the investigative site as an Annex to Protocol document, and is maintained within the Site Master File.

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

In addition, there are certain circumstances in which durvalumab should be permanently discontinued (see Section 7.1 of this protocol and the TMGs). In such circumstances, a determination of the relationship between AZD4635 and toxicity should be discussed with Medical Monitor and/or Sponsor. In the absence of a clear relationship to AZD4635 dosing, the investigational study drug AZD4635 may be restarted as monotherapy after toxicities have resolved to baseline or Grade 1 within 8 weeks of durvalumab-related toxicity.

These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of his clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to durvalumab monotherapy regimen by the reporting Investigator.

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

Dose reductions for durvalumab are not permitted (except if participant's weight decreases to <30 kg. In case of doubt, the Investigator should consult with the Medical Monitor/AstraZeneca Study Physician.

6.7.2.2 Durvalumab Infusion-Related Reactions

In the event of an infusion-related reaction ≤ Grade 2, the infusion rate of durvalumab may be decreased by 50% or interrupted until resolution of the event and re-initiated at 50% of the initial rate until completion of the infusion (see TMGs). In participants experiencing infusion-related reactions ≤ Grade 2, subsequent infusions may be administered at 50% of the initial rate. The total allowed infusion time should not exceed 8 hours at room temperature.

If a participant experiences an infusion-related reaction, acetaminophen/paracetamol and/or an antihistamine (e.g., diphenhydramine) and/or corticosteroid or equivalent medications, per institutional standard may be administered prior to subsequent infusions at the discretion of the Investigator for secondary prophylaxis of infusion-related reactions. If the infusion-related reaction is Grade 3 or higher in severity, treatment with durvalumab will be discontinued.

As with any monoclonal antibody, allergic reactions to dose administration are possible. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis. The study site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit participants to an intensive care unit if necessary.

6.7.3 Management of Toxicities Related to Cabazitaxel Therapy

The JEVTANA (cabazitaxel) prescribing recommendations provided by the manufacturer will be applied should a participant require a dose modification, hold or supportive care for toxicity that is clearly attributable to the cabazitaxel.

Dose modifications should be made if participants experience the following adverse reactions (Grades refer to Common Terminology Criteria for Adverse Events [CTCAE], Version 5.0).

Table 12 Recommended Dose Modifications For Adverse Reactions in Participants Treated with Cabazitaxel

Toxicity	Dose modification
Prolonged grade ≥3 neutropenia (greater than 1 week) despite appropriate medication, including G-CSF	Delay treatment until neutrophil count is >1,500 cells/mm^3, then reduce of cabazitaxel dose to 20 mg/m^2. Use G-CSF for secondary prophylaxis.
Febrile neutropenia	Delay treatment until improvement or resolution, and until neutrophil count is >1,500 cells/mm^3, then reduce cabazitaxel dose to 20 mg/m^2. Use G-CSF for secondary prophylaxis.
Grade ≥3 diarrhoea or persisting diarrhoea despite appropriate medication, fluid and electrolyte replacement	Delay treatment until improvement or resolution, then reduce cabazitaxel dose to 20 mg/m^2.
Grade ≥2 peripheral neuropathy	Delay treatment until improvement, then reduce to 20 mg/m^2.

Discontinue cabazitaxel treatment if participant continues to experience any of these reactions at 20 mg/m^2.

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. Severe reactions can occur and may include generalised rash/erythema, hypotension and bronchospasm. Severe hypersensitivity reactions require immediate discontinuation of cabazitaxel and appropriate therapy.

6.8 Intervention after the End of the Study

Intervention after the end of the study will be at the discretion of the Investigator.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

Any participant who discontinues one or more IP, but not the other(s), may continue on study and normal study assessments will continue, if the Investigator believes the participant is receiving benefit.

It may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for follow-up. See the SoA for data to be collected when study intervention is discontinued (e.g., end of treatment visit) and follow-up and for any further evaluations that need to be completed. Study intervention discontinuation will be reported to the IWRS by the site.

Participants may be discontinued from study intervention in the following situations. Note that discontinuation from study intervention is NOT the same thing as complete withdrawal from the study intervention. Participants who discontinue from study intervention should continue the study (i.e., continue with study visits and assessments). Reasons for study intervention discontinuation include:

- Participant decision. The participant is at any time free to discontinue study intervention without prejudice to further treatment
- Any AE that in the opinion of the Investigator or AstraZeneca, contraindicates further dosing or meets the criteria for discontinuation as defined in the dose modification guidance or prescribing information for the study intervention(s).
- Confirmed disease progression unless in the opinion of the Investigator, the participant is still receiving clinical benefit. Participants will continue study intervention until objective disease progression, or beyond RECIST v1.1 defined progression if participant is receiving clinical benefit, as judged by the Investigator and in the absence of discontinuation criteria. Tumour assessments must continue while participant continues to receive study treatment as per Section 8.1.1.
- Investigator decision or severe non-compliance with the CSP as judged by the Investigator and/or AstraZeneca
- Participant started alternative anticancer therapy including another investigational agent
- Participant lost to follow-up.

Participants may withdraw from any aspects of the voluntary genetic research (see Section 8.7) at any time, without prejudice to further treatment and independent of any decision concerning participation in other aspects of the main study.

See the SoA for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.1 Procedures for Discontinuation of Study Intervention

The Investigator should instruct the participants to contact the site before or at the time if study intervention is stopped. A participant that decides to discontinue study intervention will always be asked about the reason(s) and the presence of any AEs. The date of last intake of study intervention should be documented in the electronic CRF (eCRF) and reported to the IWRS. All study interventions should be returned by the participant at their next on-site study visit or unscheduled visit. Participants permanently discontinuing study treatment should be given locally available standard of care therapy, at the discretion of the Investigator.

Discontinuation of study intervention, for any reason, does not impact on the participant´s participation in the study. The participant should continue attending subsequent study visits and data collection should continue according to the study protocol. If the participant does not agree to continue in-person study visits, a modified follow-up must be arranged to ensure the collection of endpoints and safety information. This could be a telephone contact with the participant, a contact with a relative or treating physician, or information from medical records. The approach taken should be recorded in the medical records. A participant that agrees to a modified follow-up is not considered to have withdrawn consent or to have withdrawn from the study.

7.2 Participant Withdrawal from the Study

A participant may withdraw from the study at any time at his own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioural, compliance, or administrative reasons. This is expected to be uncommon.

A participant who considers withdrawing from the study must be informed by the Investigator about modified follow-up options (e.g., telephone contact, a contact with a relative or treating physician, or information from medical records).

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

A participant who withdraws consent will always be asked about the reason(s) and the presence of any AEs. The Investigator will follow up participants as medically indicated.

AstraZeneca or its delegate will request Investigators to collect information on participants' vital status (dead or alive; date of death when applicable) from publicly available sources at the end of the study, in accordance with local regulations. Knowledge of the vital status of all participants at study end is crucial for the integrity of the study.

If a participant withdraws from the study, it should be confirmed if he still agrees for existing samples to be used in line with the original consent. If he requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried out in line with what was stated in the informed consent and local regulation. The Investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.

During the study, COVID-19 tests may be prescribed, if required, and in accordance with local guidance. If a participant tests positive, his continued participation in the study and his treatment with the study drugs will be discussed with the Parexel and AstraZeneca Medical Monitors for this study.

See the SoA (Table 1 or Table 2) for data to be collected at the time of study intervention discontinuation and follow-up and for any further evaluations that need to be completed. All study treatment should be returned by the participant.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and are unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Efforts to reach the participant should continue until the end of the study. Should the participant be unreachable at the end of the study, the participant should be considered to be lost to follow-up with unknown vital status and censored at latest follow-up contact. As for withdrawn participants (see Section 7.2), Investigators will be requested to collect information of the survival status of participants lost to follow-up (see Section 8.2.10.3). If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix A.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in the SoA. Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (e.g., blood count), and obtained before signing of the ICF, may be utilised for screening or baseline purposes - provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

The amount of blood collected from each participant during the first 2 treatment cycles, including any extra assessments that may be required, will not exceed approximately 160 mL in Arm A and approximately 228 mL in Arm B. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Efficacy Assessments

Evaluation of objective tumour response in this study will be done using RECIST v1.1 criteria in evaluable soft tissue disease. Tumours will be assessed at screening according to the treatment arm schedule of assessments. Reassessment of tumours will be done by the same methods used to establish baseline tumour measurements.

PCWG3 PSA criteria will also be used to evaluate response and progression. These criteria will be followed for determining the change in PSA levels. Prostate-specific antigen levels in this study will be measured at screening, at the start of each new treatment cycle, at the end of treatment (EOT) visit, at any other time points indicated in the SoA, and as clinically indicated.

Disease progression will be deemed to have occurred if 1 or more of the following criteria is met:

- Soft tissue disease progression as defined by RECIST v1.1

- Bone lesion progression by PCWG3 (Table 13)
- Death

Participants with PSA progression are permitted and encouraged to continue treatment until radiographic progression. Sites should monitor PSA by cycle but plan to continue through early rises for a minimum of 12 weeks unless there is other evidence of progression.

8.1.1 Tumour Assessments with RECIST v1.1

RECIST v1.1 guidelines for measurable and non-measurable target lesions (TLs) and non-target lesions (NTLs) and the objective tumour response criteria are presented in Appendix F.

Baseline tumour assessments should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual participants. Baseline assessments should be performed no more than 28 days before the start of study treatment, and ideally should be performed as close as possible to the start of study treatment. The methods of assessment used at baseline should be used at each subsequent follow-up assessment. 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).

For **Arm A** (AZD4635 plus durvalumab), the first follow-up assessment should be after Cycle 2 (8 weeks). Follow-up assessments should be performed every 8 weeks ±1 week from the start of dosing for the first 24 weeks and then every 12 weeks (±1 week) thereafter. Any other sites at which new disease is suspected should also be appropriately imaged. If an unscheduled assessment is performed and the participant has not progressed, every attempt should be made to perform subsequent assessments at the scheduled visits.

For **Arm B** (AZD4635 plus durvalumab and cabazitaxel), the first follow-up assessment should be after Cycle 3 (9 weeks). 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) thereafter. Any other sites at which new disease is suspected should also be appropriately imaged. If an unscheduled assessment is performed and the participant has not progressed, every attempt should be made to perform subsequent assessments at the scheduled visits.

Categorisation of objective tumour response assessment will be based on the RECIST v1.1 guidelines for response of soft tissue lesions: CR (complete response), PR (partial response), SD (stable disease), and PD (progression of disease). For participants who only have NTLs at baseline, categorisation of objective tumour response assessment will be based on the RECIST v1.1 guidelines for response for NTLs: CR, PD, and Non CR/Non PD.

If the Investigator is in doubt as to whether progression has occurred, particularly with response to NTLs or the appearance of a new lesion, it is advisable to continue treatment and reassess the participant's status at the next scheduled assessment or sooner if clinically indicated.

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

Calculation or derivation of tumour response variables

At each visit, participants will be programmatically assigned a RECIST visit response of CR, PR, SD, non-CR/non-PD, or PD depending on the status of their disease compared to baseline and previous assessments.

Progression of TLs will be calculated in comparison to when the tumour burden was at a minimum (i.e., smallest sum of diameters previously recorded on study, nadir). In the absence of progression, tumour response (CR, PR, SD) will be calculated in comparison to the baseline tumour measurements obtained before starting treatment.

If a participant has had a tumour assessment that cannot be evaluated, then the participant will be assigned a visit response of no evaluable (NE), unless there is evidence of progression in which case the response will be assigned as PD.

Objective response rate is defined as the proportion of participants with measurable disease at baseline who have a confirmed CR or PR per RECIST v1.1. For the analysis of ORR an "evaluable-for-response" population will be derived and will exclude participants who do not have measurable disease at baseline.

A visit response of CR is defined when all TL and NTL lesions present at baseline have disappeared (with the exception of lymph nodes which must be <10 mm to be considered non-pathological) and no new lesions have developed since baseline. A visit response of PR is defined when the sum of diameters of the TLs has decreased by 30% or more compared to baseline (with no evidence of progression) and the NTLs are at least stable with no evidence of new lesions.

In the case of SD (participants who have neither progressed nor achieved at least a PR and are evaluable), measurements should have met the SD criteria at least once after the study start.

When the Investigator is in doubt as to whether PD has occurred and therefore reassesses the participant at a later date, the date of the initial scan should be declared as the date of

progression if the repeat scans confirm progression.

Percentage change from baseline in tumour size will be determined for participants with measurable disease at baseline and is derived at each visit by the percentage change in the sum of the diameters of TLs.

8.1.2 PCWG3 Bone Lesion Assessment

Categorisation of tumour progression of bone lesions will be based on the PCWG3 criteria. Bone lesions will be assessed by bone scintigraphy commonly performed with technetium-99 (bone scans). Positive hot spots on the bone scan should be considered significant and unequivocal sites of malignant disease to be recorded as metastatic bone lesions (see Table 13).

Table 13 Requirements for Documentation of Progression

Visit Date	Criteria for Bone Progression	Criteria for Soft Tissue Progression
First visit after baseline (expected Week 8 /Arm A* and Week 9 /Arm B*)	– 2 or more new lesions compared to baseline bone scan. – Requires confirmation at least 8/9 weeks later with ≥2 additional lesions compared to the first scan after baseline	– Progressive disease on CT or MRI by RECIST v1.1 – Requires confirmation at least 3/4 weeks (but no more than 8/9 weeks).
From the 2nd visit onwards post-baseline	– 2 or more new lesions compared to the first bone scan after baseline. – Requires confirmation at least 8/9 weeks later for persistence or increase in number of lesions	– Progressive disease on CT or MRI by RECIST v1.1 – No confirmation required.

CT, Computed tomography; MRI, Magnetic resonance imaging; RECIST, Response Evaluation Criteria in Solid tumours.
*Timing for Arm A and Arm B response confirmation or response will be different based on cycle length.

CCI [redacted]

8.1.4 PCWG3 PSA Criteria

All participants should have PSA collected at screening, at the start of each new treatment cycle, at the end of study treatment, and as indicated in the SoA (see Table 1 and Table 2).

PSA should also be collected when clinically indicated as per Investigator discretion.

PCWG3 PSA criteria are located in Appendix H.

8.2 Safety Assessments

8.2.1 Physical Examinations 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 SoA (Table 1 and Table 2). Physical examinations will include assessments of the head, eyes, ears, nose, and throat and the respiratory, cardiovascular, gastrointestinal, urogenital, musculoskeletal, neurological, dermatological, hematologic/lymphatic, and endocrine systems. Height will be measured at screening only. Investigators should pay special attention to clinical signs related to previous serious illnesses. New or worsening abnormalities may qualify as AEs. See Section 8.3 for details.

8.2.2 Performance Status

World Health Organisation (WHO) performance status will be documented as indicated in the treatment arm SoA (Table 1 and Table 2).

Table 14 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

8.2.3 Vital Signs and Height

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 SoA (Table 1 and Table 2).

8.2.4 Electrocardiograms

Electrocardiograms (ECGs) will be obtained at screening and when clinically indicated.

Resting 12-lead ECG

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 SoA (see Table 1 and Table 2). 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. Triplicate ECGs should be taken about a minute apart within a 5-minute window per time point. A standardized ECG machine should be used, and the participant should be examined using the same machine throughout the study, when feasible.

The ECG traces will be recorded and reviewed. The Investigator or designated physician will review each of the ECGs and may refer the participant to a local cardiologist, if appropriate. If an abnormal ECG finding at screening or baseline is considered to be clinically significant by the Investigator, it should be reported as a concurrent condition. 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). For all ECGs, details of rhythm, PR, R-R, QRS and QT intervals and an overall evaluation will be recorded.

8.2.5 Echocardiogram/MUGA

An echocardiogram or MUGA scan will be conducted on all participants at screening. The screening echocardiogram or MUGA scan will not be required if a previous echocardiogram or MUGA scan was performed 6 months prior to screening, unless there has been a change in the participant's cardiac status. Additional assessments for echocardiogram or MUGA during the study will be determined as clinically indicated based on the current available data.

8.2.6 Concomitant Medications

All concomitant medications and prescribed, over-the-counter, or natural/herbal remedies taken or administered 28 days prior to the first dose of AZD4635 through 30 days after the last dose of study intervention must be recorded. Concomitant medications (cancer therapy only) will also be recorded at the 90-day follow-up and the progression-free survival follow-up visits to capture subsequent cancer therapy.

8.2.7 Clinical Safety Laboratory Assessments

See Table 15 for the list of clinical safety laboratory tests to be performed, the screening tests, and the treatment arm SoA (Table 1 and Table 2) for the timing and frequency. All protocol-required laboratory assessments, as defined in the table, must be conducted in accordance with the Laboratory Manual and the SoAs.

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at the study centre as source data for laboratory variables.

For information on how AEs based on laboratory tests should be recorded and reported, see Section 6.7.

Table 15 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
Additional Tests	Potassium
Prostate specific antigen (PSA)	Sodium
CCI	Total bilirubin[b]
Testosterone	Total protein
C-reactive protein (CRP)	Urea nitrogen
	Uric acid
	Thyroid stimulating hormone (TSH)[f]
	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 data management 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.

Note: In case a participant shows an AST or ALT ≥ 3 × ULN together with total bilirubin ≥2xULN please refer to Appendix E 'Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law', for further instructions.

8.2.8 Other Assessments

Prostate-specific antigen (PSA) CCI [redacted] Blood samples will be collected for PSA CCI [redacted] assessment at baseline and at the start of each new treatment cycle, at the end of study treatment, and at progression. The PSA CCI [redacted] samples will be analysed by a local laboratory and a central laboratory, respectively.

Testosterone level must be <50 ng/mL at the screening visit.

COVID-19 testing

During the study, COVID-19 tests may be prescribed, if required, and in accordance with local guidance. If a participant tests positive, his continued participation in the study and his treatment with the study drugs will be discussed with the Parexel and AstraZeneca Medical Monitors for this study.

8.2.9 Clinical Outcome Assessments

A Clinical Outcome Assessment (COA) is any assessment that may be influenced by human choices, judgement, or motivation and may support either direct or indirect evidence of treatment benefit. Patient Reported Outcomes (PROs) is one of the types of COAs.

PROs, an umbrella term referring to all outcomes and symptoms, are directly reported by the participant. PROs have become a significant endpoint when evaluating effectiveness of treatments in clinical trials.

The following PRO instruments will be administered for analysis of the PRO endpoints at the

start of each visit, as per the Schedule of Activities (Section 1.3): BPI-SF and FACT-P. Each is described below.

Brief Pain Inventory – Short Form

Worst pain, average pain and pain's interference with daily life will be assessed during the study intervention using the (Brief Pain Inventory – Short Form) BPI-SF (see Appendix J) 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.

FACT-P

The FACT-P was developed to measure health related quality of life (HRQL) in men with prostate cancer (Esper et al. 1997, Cella et al 1993). 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 (see Appendix K).

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), 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]

8.2.10 Follow-up Visits

8.2.10.1 30-day and 90-day Follow-up Visits

A safety follow-up visit will be performed approximately 30 (± 7) days and 90 (± 7) days after the study intervention(s) are permanently discontinued. The primary purpose of the follow-up visits is to assess any AEs ongoing at the time of study intervention discontinuation and to assess any new AEs that may have occurred since discontinuation. In addition, any new medications will be recorded. This information can be collected by phone. Any AE, SAE, or abnormal laboratory findings that are ongoing at the time of study intervention discontinuation, or any new events within 30 or 90 days of last study intervention unless

otherwise indicated in the protocol, must be followed up to resolution or until the event becomes stable (or returns to baseline) or is unlikely to resolve further in the opinion of the Investigator.

8.2.10.2 Progression-free Follow-up Visits

Participants who discontinue study intervention prior to the occurrence of objective PD will be followed with PSA samples and CT/MRI/positron emission tomography (PET) scans and bone scans, and COAs (BPI-SF and FACT-P) every 12 weeks (±1 week) 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.

8.2.10.3 Survival Follow-Up

Participants will be followed every 3 months after the last dose of study intervention for survival and subsequent cancer therapy until the final DCO for the relevant arm. The survival follow-up can be done by a medical record review or telephone call at the Investigator's discretion.

Note: when required 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 after the DCO date these participants will be censored at the date of DCO. When required 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.

8.3 Adverse Events and Serious Adverse Events

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

The definitions of an AE or SAE can be found in Appendix B.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorised representative).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

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.

If the Investigator becomes aware of an SAE with a suspected causal relationship to the investigational medicinal product that occurs after the end of the clinical study in a participant treated by him or her, the Investigator shall, without undue delay, report the SAE to the sponsor.

8.3.2 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs/non-serious AEs/AEs of special interest (AESIs) (as defined in Appendix B), will be followed until resolution, stabilisation, the event is otherwise explained, or the participant is lost to follow-up.

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

Adverse event variables

The following variables will be collected for each AE;

- AE (verbatim)
- The dates when the AE started and stopped
- CTCAE, Version 5.0 grade/maximum CTCAE grade
- Whether the AE is serious or not
- Investigator causality rating against the IP(s) (yes or no)
- Action taken with regard to IP(s)
- Action taken with regard to procedure or concomitant medication
- Outcome
- Does the Investigator consider this AE an imAE?

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

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death

- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment in relation to other medication

8.3.3 Causality Collection

In this protocol the investigational products are AZD4635, durvalumab and cabazitaxel. The Investigator should assess causal relationship between IP and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

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

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

8.3.4 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant or reported in response to the open question from the study site staff: 'Have you had any health problems since the previous visit/you were last asked?', or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.3.5 Adverse Events Based on Examinations and Tests

The results from the Clinical Study Protocol mandated laboratory tests and vital signs will be summarised in the Clinical Study Report (CSR).

Deterioration as compared to baseline in protocol mandated laboratory tests and vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria, are the reason for discontinuation of treatment with the investigational product or are considered to be clinically relevant as judged by the Investigator (which may include but are not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study intervention, e.g., dose adjustment or drug interruption).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator

uses the clinical, rather than the laboratory term (e.g., anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

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

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study.

8.3.6 Hy's Law

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

8.3.7 Disease Progression

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

8.3.8 Reporting of Serious Adverse Events

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

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate AstraZeneca representatives within one day i.e., immediately but **no later than 24 hours** of when they become aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE

within one calendar day i.e., immediately but **no later than 24 hours** of when they become aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the EDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the EDC system is not available, then the Investigator or other study site staff reports a SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the Investigator/study site staff how to proceed.

Investigators or other site personnel send relevant CRF modules by fax to the designated AstraZeneca representative.

For further guidance on the definition of a SAE, see Appendix B of the Clinical Study Protocol.

The reference document for definition of expectedness/listedness is the IB for the AstraZeneca drug, and the label such as EU SmPC, USPI or other local label for the active comparator product (including any AstraZeneca comparator.).

8.3.9 Pregnancy

Conception must be avoided during paternal exposure to AZD4635. If a pregnancy in the female partner of a participant is reported, the Investigator or other site personnel must inform the appropriate AstraZeneca representatives within 1 day i.e., immediately but **no later than 24 hours** of when they become aware of it (i.e., within 24 hours of learning of the pregnancy). Exception to this is if the pregnancy is discovered before the study participant has received any study drug. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.9.1 Paternal Exposure

Information on the pregnancy of a participant's partner must be obtained directly from the participant's partner. Therefore, prior to obtaining information on the pregnancy, the Investigator must obtain the consent of the participant's partner.

Pregnancy of a participant's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring any time from the first date of dosing for AZD4635, durvalumab and cabazitaxel until 3 months (Arm A) or 6 months (Arm B) after the last dose of the study drugs should, if possible, be followed up and documented until 30 days after birth. As deemed appropriate, the pregnancies will be followed up per local guidance and regulatory requirements.

Participants should use condoms in conjunction with spermicides with female partners during the study and for 12 weeks (3 months) after the last dose of AZD4635 and/or durvalumab and for 24 weeks (6 months) after the last dose of cabazitaxel, and refrain from donating sperm from the start of dosing until 24 weeks (6 months) after discontinuing study treatment. If not done previously, storage of sperm prior to receiving AZD4635 will be advised to male participants with a desire to have children.

It is not currently known whether AZD4635 affects fertility in humans.

AstraZeneca should be notified of any pregnancy that occurs in partners of participants during participation in studies of AZD4635.

Participants in Arm B will be advised on storage of sperm prior to receiving cabazitaxel due to the possibility of irreversible infertility/testicular damage due to cabazitaxel therapy.

When the eCRF module is used include the following: The PREGREP module in the eCRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

8.3.10 Medication error

If a medication error occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day i.e., immediately but no later than 24 hours of when they become aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within 1 (Initial Fatal/Life-Threatening or follow up Fatal/Life-Threatening) or 5 (other serious initial and follow up) calendar days if there is an SAE associated with the medication error (see Section 8.3.10) and within 30 days for all other medication errors.

The definition of a Medication Error can be found in Appendix B.

8.4 Overdose

If associated with an AE, any dose in excess of the dose specified according to the protocol will constitute an overdose. There is currently no known antidote to AZD4635, and the treatment of overdose should be supportive for the underlying symptoms. For durvalumab and cabazitaxel please refer to Section 6.5.4.

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

If an overdose on an AstraZeneca study intervention occurs in the course of the study, the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, but **no later than 24 hours** of when they become aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for overdoses associated with an SAE (see section 8.3.8) and within 30 days for all other overdoses.

8.5 Human Biological Samples

Instructions for the collection and handling of biological samples will be provided in the study specific laboratory manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. For further details on Handling of Human Biological Sample see Appendix C.

Samples will be stored for a maximum of 15 years from the date of the issue of the CSR in line with consent and local requirements, after which they will be destroyed/repatriated.

- Pharmacokinetic (PK) samples will be disposed of after the Bioanalytical Report finalisation or six months after issuance of the draft Bioanalytical Report (whichever is earlier), unless consented for future analyses.
  - Pharmacokinetic (PK) samples may be disposed of or anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled pharmacokinetic samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.
- Remaining anti-drug antibody sample aliquots will be retained at AstraZeneca or its designee for a maximum of 15 years following issue of the CSR. Additional use includes but is not limited to further characterisation of any anti-drug antibodies, confirmation and/or requalification of the assay as well as additional assay development work. The results from future analysis will not be reported in the CSR.

8.5.1 Pharmacokinetics

This section describes the schedule for collection of samples for AZD4635 and cabazitaxel PK assessments. The schedule for collection of PK samples for durvalumab is described along with the collection of anti-drug antibody samples in Section 8.5.2.

Venous blood samples (2 mL) each for AZD4635 and cabazitaxel will be collected for analyses of AZD4635 and its metabolites and cabazitaxel plasma concentration.

Sparse PK samples for AZD4635 will be collected from Arm A participants according to

Table 16. Up to approximately the first 12 evaluable Arm B participants will have additional PK samples for AZD4635 collected during Cycle 1 Day 1 and Day 2 according to Table 17. Subsequent participants entering the study will have the sparse PK schedule according to Table 18. The same 12 evaluable Arm B participants will have cabazitaxel PK samples according to Table 19.

Pre-infusion samples can be collected any time (on the same day) prior to dosing. 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.

If a participant misses any doses of study drug within 3 days prior to PK sampling, please contact the primary study contact as to any effect of the required changes on the timing of the PK assessments. All other assessments should continue to be performed as per study plan, relative to baseline assessments.

Table 16 Arm A AZD4635 Sparse PK Sampling Schedule

Cycles	Day	Collection Time
1, 3, 5, 7	1	Pre-dose

Table 17 Arm B AZD4635 PK Sampling Schedule (First 12 evaluable participants)

Cycle	Day	Collection Time
1	1	Pre-dose (and pre-infusion durvalumab) 30 minutes post-dose 1 hour post-dose 2 hours post-dose 4 hour post-dose 6 hours post-dose 8 hour post-dose
	2	24 hours post-dose
2, 3, 5 7	1	Pre-dose

Table 18 Arm B AZD4635 Sparse PK Sampling Schedule (All Participants)

Cycle	Day	Collection Time
1, 3, 5, 7	1	Pre-dose

Table 19 Arm B Cabazitaxel PK Sampling Schedule (First 12 Evaluable Participants)

Cycle	Day	Collection Time
1		Pre-dose (and pre-infusion durvalumab) 5 minutes before the end of infusion 30 minutes post-dose 1 hour post-dose 2 hours post-dose 4 hour post-dose 6 hours post-dose 8 hour post-dose
	2	24-hours post-dose

Note: The first 12 evaluable participants in Arm B will have cabazitaxel PK samples collected only during Cycle 1.

Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

8.5.1.1 Determination of Drug Concentration

Samples for determination of drug concentration (AZD4635 and metabolites, and cabazitaxel) in plasma will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

8.5.2 Immunogenicity Assessments

Collection of durvalumab pharmacokinetic and anti-drug antibody samples

Venous blood samples for determination of concentrations of durvalumab (3.5 mL) and anti-drug antibodies (5 mL) in serum will be taken at the times presented in Table 20 below:

Table 20 Durvalumab PK and Anti-Drug Antibody Sampling Times

Cycle/Day	PK Sample Collection Time	Anti-drug Antibody Sample Collection Time
Cycle 1 Day 1	Pre-infusion and end of infusion	Pre-infusion
Cycle 2 Day 1	Pre-infusion	Pre-infusion
Cycle 4 Day 1	Pre-infusion and end of infusion	Pre-infusion
Cycle 7 Day 1	Pre-infusion	Pre-infusion
Follow-up Visit	90 days post last dose	90 days post last dose

Samples for determination of durvalumab concentration in serum will be analysed by a designated third party on behalf of AstraZeneca. Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual. Full details of the analytical method used will be described in a separate Bioanalytical Validation Report.

All durvalumab PK samples need to be collected within 10% of the nominal time (e.g., ± 6 minutes for a 60-minute sample) to be protocol compliant. The timing of the PK and anti-drug antibody samples may be adjusted during the study, dependent on emerging data, in order to ensure appropriate characterisation of the plasma concentration-time profiles.

Blood samples for determination of anti-drug antibody in serum will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Full details of the methods used will be described in a separate report.

Anti-drug antibody samples may also be further tested for characterisation of the anti-drug antibody response.

Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

8.5.3 Pharmacodynamics

Pharmacodynamic biomarkers are detailed in Section 8.6.

8.6 Human Biological Sample Biomarkers

Mandatory collection of samples for biomarker research is a part of this study. The following samples for biomarker research are required and will be collected from all participants in this study as specified in the SoA (Table 1 and Table 2).

CCI [redacted]

CCI [redacted]

8.6.1.2 Collection of Plasma Samples for Circulating Tumour DNA

CCI [redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

CCI [redacted]

[redacted]

8.7 CCI [redacted]

[redacted]

[redacted]

[redacted]

8.8 Health Economics

Health Economics parameters are not evaluated in this study.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

The study is non-comparative so there will be no formal statistical hypotheses. The analysis for the study will be descriptive.

9.2 Sample Size Determination

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. CCI

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

CCI

A futility interim analysis will be carried out as described in Section 9.5.

9.3 Populations for Analyses

For purposes of analysis, the following populations are defined:

Table 21 Populations for Analysis

Population/Analysis set	Description
Evaluable for efficacy	Dosed participants with a baseline tumour assessment.
Tumour response	Dosed participants with a baseline tumour assessment, and measurable disease at baseline.
Safety analysis set	All participants who received at least 1 dose of study drug
PSA evaluable	Dosed participants with an abnormal baseline PSA (≥1ng/mL)
Pharmacokinetics	Dosed participants for whom an adequate PK profile has been obtained

9.4 Statistical Analyses

Analyses will be performed by Parexel under the direction of the Oncology Biometrics, AstraZeneca. A comprehensive statistical analysis plan will be developed and finalised before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints. Any deviations from this plan will be reported in the CSR.

9.4.1 General Considerations

The main aims of the study are to assess the efficacy, safety, and tolerability of multiple study drugs in participants with prostate cancer. 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.

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. Participant 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.

9.4.1.1 Primary Endpoint

The primary efficacy endpoint is rPFS defined as the time from first dose until radiographic progression as assessed by the Investigator per RECIST v1.1 (soft tissue) and PCWG3 (bone) or death from any cause, whichever comes first.

9.4.1.2 Secondary Endpoints

Secondary endpoints include: safety, OS, ORR, DoR, PSA50 response, time to pain progression, and PK. The analysis will be descriptive and summaries will be presented for Arm B. Data from Arm A will be listed only.

The primary endpoint (ie, rPFS) will be summarised by ADO signalling gene expression in high and low subgroups in Arm B.

9.4.2 Efficacy

Radiological progression-free survival (rPFS)

Progression-free survival is 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.

However, if the participant progresses or dies after 2 or more missed radiologic visits the participant will be censored at the time of the last evaluable RECIST v1.1 or bone scan assessment prior to the 2 missed visits. If a participant has an assessment for soft tissue disease (MRI/CT) but not for bone disease (bone scan), or vice versa, then this will count as a missed assessment. If the participant has no evaluable post-baseline RECIST v1.1 or bone scan assessments 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).

Progression-free survival will be derived based on scan/assessment dates not the scheduled visit dates. If RECIST v1.1 assessments/bone scans contributing toward a particular visit are performed on different dates then the date of progression will be determined based on the earliest of the dates of the component that triggered the progression. With regard to censoring, a participant will be censored at the latest of the dates contributing to a particular overall visit assessment. Summaries (number of events, medians, proportion and 95% CI for progression free at fixed time points using the Kaplan-Meier estimate) and Kaplan-Meier plots will be provided. A 2-sided 95% CI for the median PFS will be produced in addition to the 25^{th} and 75^{th} percentiles.

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. Any participant not known to have died at the time of analysis will be censored based on the last recorded date on which the participant was known to be alive.

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 after the DCO date these participants will be censored at the date of DCO.

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

Tumour response

Tumour response data will be summarised for dosed participants with measurable disease at baseline, and separately for dosed participants with measurable or non-measurable disease at baseline.

Tumour response data will be listed using the following response categories: CR, PR, SD, Non-CR/Non-PD, PD, and not evaluable (NE).

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 responder will be any participant with a confirmed response of PR or CR in their soft tissue disease assessed by RECIST 1.1, in the absence of progression on bone scan assessed by PCWG3. 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).

Best objective response and confirmed ORR will be summarised. The BOR table will be presented for the evaluable for efficacy analysis set and separately for the tumour response analysis set. The tumour analysis set will be used for ORR. The proportion of participants achieving an 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). Percentage change from baseline in tumour size will be determined for participants with measurable disease at baseline and is derived at each visit by the percentage change in the sum of the diameters of TLs.

Waterfall plots (bar plots), and 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. 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.

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. The end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. The time of the initial

response will be defined as the latest of the dates contributing towards the first visit that was PR or CR that was subsequently confirmed.

Duration of response will be analysed in the same manner as PFS if the number of participants with DOR allows. In addition, Swimmer plots will be produced.

If a participant does not progress following a response, then their duration of response will use the PFS censoring date as the date at which that participant is censored for DoR.

CCI [redacted]

PSA response

PSA_{50} response is 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. Ignore early rises (before 12 weeks) in determining PSA response.

- 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.

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

Patient Reported Outcomes

For analysis of the PRO endpoints, BPI-SF, FACT-P, the following analysis will be performed and will be reported in the CSR.

Summary statistics for mean score, standard deviation, median and range will be presented by treatment group for visits until there are less than one third of participants with evaluable data. 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).

Time to deterioration will be assessed using the same methods as for the primary analysis. Kaplan-Meier plots will be presented for each treatment arm.

In addition the time to deterioration for the subscales of the FACT-P (TOI, FAPSI-6, PCS and FWB) will be presented.

9.4.3 Safety

Safety data will not be formally analyzed but appropriate summaries for safety data 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).

Data from all cycles of initial treatment will be presented as described in the Statistical Analysis Plan. Adverse events will be listed individually by participant and dose group. For participants who have a dose modification, all AEs (due to drug or otherwise) will be assigned to the initial dose group. 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. The number and percentage of participants with AEs in different categories (e.g., causally related, CTCAE Grade ≥ 3, etc.) will be summarised by dose group, and events in each category will be further summarised by MedDRA system organ class and preferred term, by dose group. 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 follow-up period after discontinuation of IP will be listed separately, but not included in the summaries.

Haematology, clinical chemistry, vital signs, ECG data, ECHO/MUGA, demographic data, medical histories, and concomitant medications will be listed individually by participant and suitably summarised. For all laboratory variables, which are included in the current version of CTCAE, the CTCAE grade will be calculated. Summary statistics of mean, median, standard deviation, minimum, maximum and number of observations will be used.

Details of any deaths will be listed for all participants.

9.4.4 Other Analyses

CCI [redacted]

9.4.4.1 Pharmacokinetic Analysis

Pharmacokinetic analysis of the plasma concentration data for AZD4635 and its metabolite(s), and cabazitaxel, will be determined by Covance on behalf of the Clinical Pharmacokinetic Alliance, AstraZeneca R&D. The actual sampling times will be used in the parameter calculations and PK parameters will be derived using standard non-compartmental methods in Phoenix® WinNonlin® Version 8.1 or higher. Durvalumab PK parameters derivation is not planned due to a sparse sample collection schedule. Durvalumab predose and end of infusion concentrations will be summarised only.

Where possible the following single dose PK parameters will be determined for AZD4635, its metabolites (SSP-005173 and SSP-005174) and cabazitaxel.

- Maximum observed plasma concentration (C_{max}) and time to C_{max} (t_{max})
- Time of the last measurable concentration (t_{last})
- Terminal elimination rate constant (λz)
- Terminal half-life ($t1/2\lambda z$)
- Area under the plasma concentration time curve from zero to 24 hours [$AUC_{(0-24)}$], from zero to 8 hours [$AUC_{(0-8)}$], from zero to the time of the last measurable concentration (AUC_{last}), and from zero extrapolated to infinity (AUC_{inf}).
- Apparent plasma clearance (CL/F for AZD4635, CL for cabazitaxel)
- Apparent volume of distribution during the terminal phase (Vz/F for AZD4635, Vz for cabazitaxel)
- Mean residence time (MRT)

C_{max}, t_{max}, and t_{last} will be determined directly by inspection of the concentration-time profiles. Where possible, λz will be calculated by log-linear regression of the terminal portion of the concentration-time profiles where there are sufficient data and $t½\lambda z$ will be calculated as ln 2/ λz. $AUC_{(0-8)}$, $AUC_{(0-24)}$, and AUC_{last} will be calculated using the linear up/log down trapezoidal rule. Where appropriate, AUC_{last} will be extrapolated to infinity using λz to obtain AUC_{inf}. CL/F and CL will be determined as the ratio of dose/AUC_{inf}. Vz/F and Vz will be determined from the ratio of CL/F or CL to λz.

Additional PK parameters, including parameters for AZD4635 metabolites, may be

determined where appropriate. CCI [redacted]

9.5 Interim Analyses

Given the limited data available with the triplet combination, a futility interim analysis is planned for Arm B based on PSA_{50} 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. Further details will be provided in the SAP. 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 PSA_{50} 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.

9.6 Data Monitoring Committee

Data monitoring committee will not be used.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organisations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorisations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO, but the accountability remains with AstraZeneca.

Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.
- For all studies except those utilizing medical devices Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the [Investigator's Brochure or state other documents] and will notify the IRB/IEC, if appropriate according to local requirements.

A 2 Financial Disclosure

Investigators and sub-Investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 3 Informed Consent Process

The Investigator or his representative will explain the nature of the study to the participant or his legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the participant legally authorized representative.

CCI [redacted]

If a participant's partner becomes pregnant during or within 3 months (or as indicates in module-specific) after the study, the partner is asked to sign the "Adult Study ICF for Pregnant Partners of Study Patients" and provide information about the pregnancy accordingly.

CCI [redacted]

CCI [redacted]

A 4 Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent
- The participant must be informed that his medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Committees Structure

The safety of all AstraZeneca clinical studies is closely monitored on an on-going basis by AstraZeneca representatives in consultation with Participant Safety. Issues identified will be addressed; for instance this could involve amendments to the Clinical Study Protocol and letters to Investigators.

A 6 Dissemination of Clinical Study Data

A description of this clinical trial will be available on http://astrazenegrouptrials.pharmacm.com and http://www.clinicaltrials.gov as will the summary of the main study results when they are available. The clinical trial and/or summary of main study results may also be available on other websites according to the regulations of the countries in which the study is conducted.

A 7 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organisations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

A 8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the eCRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the clinical trial agreement.

A 9 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organisation(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participants and should assure appropriate participants therapy and/or follow-up.

Participants from terminated sites will have the opportunity to be transferred to another site to continue the study.

A 10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

B 1 Definition of adverse events

An adverse event is the development of any untoward medical occurrence in a participant or clinical study participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no Study treatment has been administered.

B 2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-participant hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity.
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the participant or may require medical treatment to prevent one of the outcomes listed above.

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate AstraZeneca representatives within one day i.e., immediately but **no later than 24 hours** of when they become aware of it.

Adverse Events (AEs) for new malignant tumours reported during a study should generally be assessed as Serious AEs. If no other seriousness criteria apply, the ‘Important Medical Event’ criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a Non-Serious AE. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfil the attributes for being assessed as serious, although reporting of the progression of the malignant tumour as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a

routine treatment that does not require hospitalisation, may be assessed as Non-Serious; examples include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

The above instruction applies only when the malignant tumour event in question is a new malignant tumour (i.e., it is *not* the tumour for which entry into the study is a criterion and that is being treated by the IP under study and is not the development of new or progression of existing metastasis to the tumour under study). Malignant tumours that – as part of normal, if rare, progression – undergo transformation (e.g., Richter's transformation of B cell chronic lymphocytic leukaemia into diffuse large B cell lymphoma) should not be considered a new malignant tumour.

Life threatening

'Life-threatening' means that the participant was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the participant's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical treatment

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardise the participant or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm

- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

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

B 3 A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the participant actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression

'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

B 4 Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study intervention that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error.

- occurred
- was identified and intercepted before the participant received the drug
- did not occur, but circumstances were recognised that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed eg, kept in the fridge when it should be at room temperature
- Wrong participant received the medication (excluding IVRS/IWRS errors)
- Wrong drug administered to participant (excluding IVRS/IWRS errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IVRS/IWRS - including those which lead to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s) eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AstraZeneca product

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

B 5 Adverse Events of Special Interest

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the Investigational Product and may require close monitoring. 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. These AESIs are being closely monitored in clinical studies with durvalumab monotherapy and combination therapy. An immune-mediated adverse event (imAE) is defined as an AESI that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE.

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

AESI/imAEs observed with anti PD-L/PD-1 agents such as durvalumab include pneumonitis, hepatitis, diarrhoea/colitis, intestinal perforation, endocrinopathies (hypo- and hyper-thyroidism, adrenal insufficiency, hypophysitis/hypopituitarism and Type 1 diabetes mellitus), nephritis, rash/dermatitis, myocarditis, myositis/polymyositis, pancreatitis and rare/less frequent imAEs including neuromuscular toxicities such as myasthenia gravis and Guillain-Barre syndrome.

Other inflammatory responses that are rare/less frequent with a potential immune-mediated

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

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

Appendix C Handling of Human Biological Samples

C 1 Chain of custody

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

The Investigator at each centre keeps full traceability of collected biological samples from the participants while in storage at the centre until shipment or disposal (where appropriate) and records relevant processing information related to the samples whilst at site.

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

AstraZeneca or delegated representatives will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca Team during for the remainder of the sample life cycle.

If required, AstraZeneca will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is the sooner.

C 2 Withdrawal of Informed Consent for donated biological samples

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

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The Investigator:

- Ensures participant's[2] withdrawal of informed consent to the use of donated samples is highlighted immediately to AstraZeneca or delegate.
- Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented
- Ensures that the participant and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organisation(s) holding the samples is/are informed about the

withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action documented and study site notified.

C 3 International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) (**https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx**) classifies infectious substances into 3 categories: Category A, Category B or Exempt

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals.
Category A pathogens are e.g., Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900:

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are e.g., Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - Substances which do not contain infectious substances or substances which are unlikely to cause disease in humans or animals are not subject to these Regulations unless they meet the criteria for inclusion in another class.

- Clinical study samples will fall into Category B or exempt under IATA regulations
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (https://www.iata.org/whatwedo/cargo/dgr/Documents/DGR-60-EN-PI650.pdf).
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content

Appendix D Optional Genomics Initiative Sample

D 1 Use/analysis of DNA

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

CCI [redacted]

[redacted]

- CCI [redacted]

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- CCI [redacted]

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Appendix E Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

E 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report Potential Hy's Law (PHL) cases and Hy's Law (HL) cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a participant meets potential PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory **and/or** elevated TBL from a local laboratory.

The Investigator will also review Adverse Event data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Serious Adverse Events (SAEs) and Adverse Events (AEs) according to the outcome of the review and assessment in line with standard safety reporting processes.

E 2 Definitions

Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) **together with** Total Bilirubin (TBL) ≥ 2xULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

Hy's Law (HL)

AST or ALT ≥ 3x ULN **together with** TBL ≥ 2xULN, where no other reason, other than the

IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (i.e., on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

E 3 Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any participant who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3xULN
- AST ≥ 3xULN
- TBL ≥ 2xULN

Local laboratories being used:

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative
- Determine whether the participant meets PHL criteria (see Section E 2 Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory eCRF

E 4 Follow-up

E 4.1 Potential Hy's Law Criteria not met

If the participant does not meet PHL criteria the Investigator will:

- Inform the AstraZeneca representative that the participant has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

E 4.2 Potential Hy's Law Criteria met

If the participant does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study

treatment (See Section E 6).

- Notify the AstraZeneca representative who will then inform the central Study Team.
- Within 1 day of PHL criteria being met, the Investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting.
- For participants that met PHL criteria prior to starting IMP, the Investigator is not required to submit a PHL SAE unless there is a significant change# in the participant's condition.
- The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study participants' follow-up (including any further laboratory testing) and the continuous review of data.
- Subsequent to this contact the Investigator will:
  - Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
  - Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Study Physician.
  - Complete the three Liver eCRF Modules as information becomes available

A **'significant' change** in the participant's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

E 5 Review and Assessment of Potential Hy's Law Cases

The instructions in this Section should be followed for all cases where PHL criteria are met.

As soon as possible after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

Where there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF
- If the alternative explanation is an AE/SAE: update the previously submitted Potential Hy's Law SAE and AE eCRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AstraZeneca standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Send updated SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provides any further update to the previously submitted SAE of Potential Hy's Law, (report term now 'Hy's Law case') ensuring causality assessment is related to IMP and seriousness criteria is medically important, according to CSP process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

E 6 Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment

This section is applicable to participants with liver metastases who meet PHL criteria on study

treatment, having previously met PHL criteria at a study visit prior to starting study treatment.

At the first on-study treatment occurrence of PHL criteria being met the Investigator will determine if there has been a **significant change** in the participants' condition[#] compared with the last visit where PHL criteria were met[#]

- If there is no significant change no action is required
- If there is a significant change, notify the AstraZeneca representative, who will inform the central Study Team, then follow the subsequent process described in Section E 4.2.

E 7 Actions Required for Repeat Episodes of Potential Hy's Law

This section is applicable when a participant meets PHL criteria on study treatment and has already met PHL criteria at a previous on study treatment visit.

The requirement to conduct follow-up, review and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The Investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

- Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study eg, chronic or progressing malignant disease, severe infection or liver disease or did the participant meet PHL criteria prior to starting study treatment and at their first on study treatment visit?

If **No**: follow the process described in Section E 4.2 for reporting PHL as an SAE

If **Yes**: Determine if there has been a significant change in the participant's condition[#] compared with when PHL criteria were previously met

- If there is no significant change no action is required
- If there is a significant change follow the process described in Section E 4.2 for reporting PHL as an SAE

A 'significant' change in the participant's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

E 8 Laboratory tests

Hy's Law lab kit for central laboratories

Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR
Viral hepatitis	IgM anti-HAV IgM and IgG anti-HBc HBsAg HBV DNA [a] IgG anti-HCV HCV RNA [a] IgM anti-HEV HEV RNA
Other viral infections	IgM & IgG anti-CMV IgM & IgG anti-HSV IgM & IgG anti-EBV
Alcoholic hepatitis	Carbohydrate deficient transferrin (CD-transferrin) [b]
Autoimmune hepatitis	Antinuclear antibody (ANA) Anti-Liver/Kidney Microsomal Ab (Anti-LKM) Anti-Smooth Muscle Ab (ASMA)
Metabolic diseases	alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin [b] Transferrin saturation

[a] HCV RNA; HCV DNA are only tested when IgG anti-HCV is positive or inconclusive
[b] CD-transferrin and Transferrin are not available in China. Study teams should amend this list accordingly

E 9 References

Aithal et al, 2011

Aithal et al 2011, Clinical Pharmacology and Therapeutics 89(6):806-815.

FDA Guidance for Industry, July 2009

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation'. Available from; https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-induced-liver-injury-premarketing-clinical-evaluation.

Appendix F Guidelines for Evaluation of Objective Tumour Response Using RECIST v1.1 in Soft Tissue

INTRODUCTION

This appendix details the implementation of RECIST (Response Evaluation Criteria in Solid Tumors) v1.1 guidelines (Eisenhauer et al. 2009) and PCWG3 guidelines (Appendix H, Scher et al. 2016) for the D8731C00002 study with regards to Investigator assessment of tumour burden including protocol-specific requirements for this study.

ASSESSMENT OF SOFT TISSUE DISEASE USING RECIST 1.1 CRITERIA

Definition of measurable, non-measurable, target and non-target lesions

Participants with at least one lesion (measurable and/or non-measurable) that can be accurately assessed at baseline by computed tomography (CT), magnetic resonance imaging (MRI) or plain X-ray should be included in this study.

Measurable:

A lesion, not previously irradiated, that can be accurately measured at baseline as ≥ 10 mm in the longest diameter (except lymph nodes which must have short axis ≥ 15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) and which is suitable for accurate repeated measurements.

Non-measurable:

- All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15mm short axis at baseline*).
- Truly non-measurable lesions include the following: leptomeningeal disease, ascites, pleural / pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by CT or MRI.
- Previously irradiated lesions**.
- Skin lesions
- Brain metastasis

*Nodes with <10mm short axis are considered non-pathological and should not be recorded or followed as NTL.

**Localized post-radiation changes which affect lesion sizes may occur. Therefore, lesions that have been previously irradiated will not be considered measurable and must be selected as Non-Target Lesions (NTL) at baseline and followed up as part of the NTL assessment.

Special Cases:

Lytic bone lesions or mixed lytic blastic lesions, with identifiable soft tissue components, can be considered measurable if the soft tissue component meets the definition of measurability. Blastic lesions are considered non-measurable.

Cystic metastases can be considered measurable lesions if they meet the criteria for measurability from a radiological point of view, but if non-cystic lesions are present in the same participant, these should be selected as target lesions.

Target lesions:

A maximum of 5 measurable lesions (with a maximum of 2 lesions per organ), representative of all lesions involved suitable for accurate repeated measurement, should be identified as target lesions (TL) at baseline.

Non-Target lesions:

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline (except bone lesions which will be assessed as defined in bone lesion section of this appendix).

Methods of assessment

The same method of assessment and the same technique should be used to characterize each identified and recorded lesion at baseline and during follow-up visits.

A summary of the methods to be used for RECIST assessment is provided below and those excluded from tumour assessments for this study are highlighted, with the rationale provided.

Table 22 Summary of Methods of Assessment

Target Lesions	Non-Target Lesions	New Lesions
CT (preferred)	CT (preferred)	CT (preferred)
MRI	MRI	MRI
	X-ray, Chest x-ray	X-ray, Chest x-ray
		Ultrasound
		FDG-PET

CT and MRI

CT and MRI are generally considered to be the best currently available and reproducible methods to measure TL selected for response assessment and to assess NTL and identification of any new lesions.

In the D8731C00002 study it is recommended that CT examinations of the chest, abdomen and pelvis will be used to assess tumour burden at baseline and follow-up visits. CT examination with intravenous (i.v.) contrast media administration is the preferred method. MRI should be used where CT is not feasible or it is medically contra-indicated.

Every effort should be made to maintain the radiologic imaging modality used at baseline throughout subsequent assessments.

X-rays

Plain X-rays

Plain X-rays may be used as a method of assessment for bone NTLs and to identify the presence of new bone lesions.

Chest X-ray

In the D8731C00002 study, chest x-ray assessment will not be used for assessment of TL as they will be assessed by CT examination or MRI examination. Chest X-ray can, however, be used to assess NTL and to identify the presence of new lesions.

Ultrasound

In the D8731C00002 study, ultrasound examination will not be used for assessment of TL and NTL as it is not a reproducible method, does not provide an accurate assessment of tumour size and it is subjective and operator dependent. Ultrasound examination can, however, be used to identify the presence of new lesions. If new clinical symptoms occur and an ultrasound is performed then new lesions should be confirmed by CT or MRI examination.

Endoscopy and laparoscopy

In the D8731C00002 study, endoscopy and laparoscopy will not be used for tumour assessments as they are not validated in the context of tumour assessment.

Tumour markers

In the D8731C00002 study tumour markers will not be used for tumour response assessments as per RECIST 1.1.

In this study the following marker (PSA) are being collected for separate analysis. However, the results will not contribute to tumour response based on RECIST 1.1 assessment.

Cytology and histology

In the D8731C00002 study histology will not be used for tumour response assessments as per RECIST 1.1 and tumour response assessments will be performed on radiological criteria only.

FDG-PET scan

In the D8731C00002 study FDG-PET scans may be used as a method for identifying new lesions, according with the following algorithm: New lesions will be recorded where there is positive FDG uptake* not present on baseline FDG-PET scan or in a location corresponding to a new lesion on CT/MRI at the same follow-up visit. If there is no baseline FDG-PET scan available, and no evidence of new lesions on CT/MRI scans then follow-up CT/MRI assessments should be continued, scheduled as per protocol or clinical indicated, in order to confirm new lesions.

* A positive FDG-PET scan lesion should be reported only when an uptake greater than twice that of the surrounding tissue is observed.

Tumour response evaluation

Schedule of evaluation

Baseline assessments should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual participants and should be performed no more than 28 days before allocation. The first follow-up assessment for 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 was performed and the participant has not progressed, every attempt should be made to perform the subsequent assessments at their originally scheduled visits. This schedule is to be followed in order to minimize any unintentional bias caused by some participants being assessed at a different frequency than other participants.

Target lesions (TL)

Documentation of target lesions

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes), representative of all lesions involved should be identified as TL at baseline. Target lesions should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis for nodal lesions), but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

The site and location of each TL should be documented as well as the longest diameter for non-nodal lesions (or short axis for lymph nodes). All measurements should be recorded in millimeters. At baseline the sum of the diameters for all TL will be calculated and reported as the baseline sum of diameters. At follow-up visits the sum of diameters for all TL will be calculated and reported as the follow-up sum of diameters.

Special cases:

- For TL measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis.
- If the CT/MRI slice thickness used is > 5mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.
- If a lesion has completely disappeared, the longest diameter should be recorded as 0 mm.
- If a TL splits into 2 or more parts, then record the sum of the diameters of those parts.
- If 2 or more TL merge then the sum of the diameters of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion(s).
- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5mm.
- If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion.
- When a TL has had any intervention e.g., radiotherapy, embolisation, surgery etc., during the study, the size of the TL should still be provided where possible.

Evaluation of target lesions

This section provides the definitions of the criteria used to determine objective tumour visit response for TL.

Table 23 Evaluation of Target Lesions

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
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD
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.
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

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Appendix H PCWG3 Criteria (Scher et al. 2016)

Baseline/Study Entry

PSA progression requirements for study entry

A sequence of rising PSA values should be obtained at least 1 week apart, with a minimum starting level of 2.0 ng/mL for trial entry. 1.0 ng/mL is acceptable as the minimum starting level for trial entry if the confirmed rise is the only indication of progression (excluding small cell carcinoma). It is recommended to estimate a pretreatment PSA doubling time (PSA-DT) if at least three values are available ≥4 weeks apart.

Baseline Imaging

Imaging of the chest, abdomen, and pelvis using a contrast-enhanced CT scan with ≤5 mm axial slices is advised for all participants. For participants that are intolerant of contrast, a cross-sectional MRI scan of the abdomen and pelvis with a noncontrast CT scan of the chest is acceptable. For Phase I and II trials, it is recommended to report whether progression on entry was in the growth of pre-existing lesions, the development of new lesions, or both. RECIST v1.1 (Eisenhauer et al. 2009) should be followed for extraskeletal disease; however, in contrast to RECIST v1.1, up to 5 lesions per site of metastatic spread can be recorded. Bone lesions should be recorded separately.

- *Prostate/prostate bed*- If there is a question of locally persistent or recurrent disease, an MRI of the prostate or prostate bed and/or biopsy of the site is recommended.

- *Nodes or viscera*- Nodal disease should be measured in the short axis and recorded by location: pelvic disease should be classified as locoregional, and extrapelvic disease (retroperitoneal, mediastinal, thoracic, or other) as metastatic. Nodes ≥1.5 cm in the short axis are considered pathologic and measurable. As per RECIST v1.1, lymph nodes ≥1.0 and less than 1.5 cm in the short axis may be pathologic and should be recorded as non-target lesions. Nodes less than 1.0 cm in the short axis are considered nonpathologic. Visceral disease in metastatic participants should be designated separately as lung, liver, adrenal, or CNS and must be ≥1.0 cm in the longest dimension per RECIST v1.1 to be included as a target lesion.

  To establish non-metastatic status in the non-metastatic castration-resistant prostate cancer (nmCRPC) population, nodes <1.0 cm in the short axis are considered nonpathologic; nodes 1.0 to less than 1.5 cm may be considered pathologic but with clinical discretion; and nodes ≥1.5 cm are both pathologic and measurable. Trial entry should be based on PSA-DT, and standard imaging modalities (bone scan, CT, and/or MRI) should be used.

- *Bone*- The use of ^{99m}Tc-methylene diphosphonate radionuclide bone scintigraphy should be used, with the presence or absence of metastasis recorded. A quantitative measure of disease burden, such as lesion number, the bone scan index, or lesion area, is recommended. Changes in lesions considered metastatic on bone scintigraphy should be followed, assessed, and recorded. Areas/lesions on bone scans that are suggestive can be assessed further with CT or MRI and followed separately, but this supplemental imaging should not be used to establish lesions for the purposes of the trial.
- *Neurologic*- It is recommended to perform an MRI or CT of the brain for participants with small cell/neuroendocrine tumours and to maintain a low threshold for performing an MRI of the base of the skull or spine to diagnose and/or detect impending neurologic compromise. Routine imaging of the brain for adenocarcinoma is not recommended.

Imaging progression requirements for study entry

- Measurable lymph nodes/lesions are not required
- Nodal progression or visceral progression independent of PSA is sufficient
- Previously normal (<1 cm) lymph nodes must have grown by ≥5 mm in the short axis from baseline or nadir and be ≥1.0 cm in the short axis to be considered to have progressed. If the node progresses to ≥1.5 cm in the short axis, it is measurable; nodes that have progressed to 1.0 to less than 1.5 cm are pathologic, subject to clinical decision, and nonmeasurable.
- For existing pathologic adenopathy, progression is defined per RECIST v1.1
- For bone involvement, there must be two new lesions. Ambiguous results should be confirmed by other imaging modalities (CT or MRI). *Note*: only positivity on the bone scan defines metastatic disease to bone.

On-Study Disease Assessments

Throughout the trial, on-treatment evaluations should include physical examinations, symptom assessments, and laboratory studies to assess safety (appropriately attributing to the disease or therapy).

Clinical symptoms, performance status, participant reported outcomes, and blood based biomarkers (PSA, alkaline phosphatase [ALP], lactate dehydrogenase [LDH], serum chemistry, complete blood count, and circulating tumour cells) should be assessed at every cycle.

Changes over time should be reported for the following blood-based biomarkers: LDH, total ALP, bone-specific ALP, urine N-telopeptide, hemoglobin, and neutrophil/lymphocyte ratio (NLR). The reported changes may include the proportion showing normalisation of a given

biomarker and/or waterfall plots of percent change from baseline in a given biomarker. Institutional normal ranges should be reported to determine normalisation of a given biomarker.

PSA

PSA should be monitored by cycle, but treatment should continue through early rises for a minimum of 12 weeks unless there is other evidence of progression, as a favorable effect on PSA may be delayed for ≥12 weeks. When determining PSA response, ignore early rises (before 12 weeks).

For control/relieve/eliminate end points:

- Record the percentage change from baseline (rise or fall) at 8-9 or 12 weeks, and separately, the maximal change (rise or fall) at any time using a waterfall plot
- Describe absolute changes in PSA over time from baseline to best response

For delay/prevent end points:

- *After decline from baseline*: record time from start of therapy to first PSA increase that is ≥25% and ≥2 ng/mL above the nadir, and which is confirmed by a second value ≥3 weeks later.
- *If no decline from baseline*:

In participants who show evidence of benefit, treatment should be continued in the case of an isolated PSA rise after an initial decline until radiographic or clinical progression is manifest.

Circulating tumour cells (CTC)

Circulating tumour cell counts should be enumerated at the start of treatment and recorded as favorable (four or fewer cells per 7.5 mL of blood) or unfavorable (five or more cells per 7.5 mL of blood). If the result was unfavorable, changes after treatment should be monitored.

For control/relieve/eliminate end points:

Report as change from unfavorable to favorable, and separately, the percent change from baseline using a waterfall plot.

For delay/prevent end points:

No validated definition exists; however, rising CTC counts are associated with a poor prognosis.

Imaging

Imaging should include cross-sectional imaging of the chest, abdomen, and pelvis, as well as bone scintigraphy, regardless of whether participants have involvement of those sites at baseline. Disease progression at new sites may be missed if imaging is restricted to known sites of disease. Imaging should be performed at fixed intervals. An 8- to 9-week assessment interval is advised for the first 24 weeks and every 12 weeks thereafter; however, there may be exceptions to these suggestions: in nmCRPC trials, for example, imaging assessment intervals of 16 weeks are advised. Likewise, in long-term responders (>2 to 3 years of clinical benefit and no signs of clinical biomarker progression), reduced frequency of imaging is reasonable, such as every 16 to 24 weeks (4 to 6 months). A favorable change noted by imaging should be confirmed with a second scan.

For control/relieve/eliminate end points:

RECIST v1.1 criteria should be followed; however, up to five lesions per site of disease can be recorded. Record changes in lymph nodes, lung, liver, adrenal, and CNS sites separately. Favorable changes should be confirmed with a second scan. Complete elimination of disease at any site should be recorded separately.

- Lymph nodes: Only report changes in lymph nodes that were measureable at baseline (≥1.5 cm in the short axis). Changes in pelvic and extrapelvic nodes should be reported separately.
- Visceral: Only report changes in lesions that were measureable at baseline (≥1.0 cm in the longest dimension). Changes in liver, lung, adrenal, and CNS should be reported separately.
- Bone: Changes should be recorded as improved, stable (no new lesions), worse (new lesions), or resolved. Changes in intensity of uptake alone do not constitute progression or regression. If there are no new lesions, therapy should be continued in the absence of other signs of progression.

For delay/prevent end points:

RECIST v1.1 criteria should be followed; however, up to five lesions per site of spread can be recorded. Record changes in lymph nodes, lung, liver, adrenal, and CNS sites separately. The type of progression (growth of existing lesions versus development of new lesions) should be recorded separately by site. The proportion of participants who have not progressed at fixed time points (6 or 12 months) should be reported.

- Note that for some treatments, a lesion may increase in size before it decreases.
- Lymph nodes: Previously normal (<1.0 cm) lymph nodes must have grown by ≥5 mm in the short axis from baseline or nadir and be ≥1.0 cm in the short axis to be considered to have progressed. Nodes that have progressed to 1.0 to less than 1.5 cm

are pathologic, subject to clinical discretion, and nonmeasureable. For existing pathologic adenopathy (≥1.5 cm), progression is defined per RECIST v1.1.

- Bone: For progression, pseudoprogression should be excluded in the absence of symptoms or other signs of progression. The 2+2 rule (at least two new lesions on the first post-treatment scan, with at least two additional lesions on the next scan) should be used to distinguish flare from true progression. If at least two additional new lesions are seen on the next (confirmatory) scan, the date of progression is the date of the first post-treatment scan (i.e. when the first two new lesions were documented). For scans after the first post-treatment scan, at least two new lesions relative to the first post-treatment scan should be confirmed on a subsequent scan. The date of progression will be the date of the scan that first documents the second lesion. Changes in intensity of uptake alone do not constitute either progression or regression. The proportion of participants who have not progressed at fixed time points (6 or 12 months) should be reported.
- .

Radiographic Progression-Free Survival (rPFS)

rPFS, defined as the time from first dose until radiographic progression, assessed by the Investigator per PCWG3 criteria (bone) or death from any cause, whichever occurs first by gene expression subgroup.

PCWG3 advises the date of progression in all specific sites be reported independently whether it is bone, nodes (pelvic or extrapelvic), visceral (lung, liver, adrenal, or CNS), or other. Reporting the proportion of patients who remain radiographic progression free at fixed time points (e.g., 6 and 12 months) is also advised.

Appendix I Disallowed Medications

The following interventions listed are restricted or prohibited and are to be used with caution or not at all as described. Exceptions may be agreed, but the circumstances must be reviewed by the Medical Monitor/AstraZeneca Study Physician in advance.

Information on any treatment in the 4 weeks prior to starting study treatment and all concomitant treatments given during the study with reasons for the treatment should be recorded.

Prohibited medications with AZD4635

Contribution of CYP1A2 to AZD4635 metabolism appears to be >80%. CYP1A2 is readily inducible by medications. The following CYP1A2 strong and moderate inducers and inhibitors (Table 24) are not permitted from 2 weeks prior to the first dose of AZD4635 until at least 2 weeks after the last dose of AZD4635.

Table 24 Examples of CYP1A2 Inhibitors and Inducers

CYP1A2	Strong inhibitors	Moderate inhibitors
	ciprofloxacin, clinafloxacin, enoxacin, fluvoxamine, oltipraz, zafirlukast, rofecoxib, Angelica root - Bai Zhi (Angelica dahurica radix)	methoxsalen, mexiletine ,oral contraceptives,3,4-methylene-dioxymethamphetamine (MDMA), etintidine, genistein, idrocilamide, osilodrostat, phenylpropanolamine, pipemidic acid, propafenone, propranolol, troleandomycin, vemurafenib, grepafloxacin, piperine, zileuton
	Strong Inducers	**Moderate Inducers**
		Phenytoin, rifampin, ritonavir, smoking, teriflunomide

Based on the potential risks for DDI, sensitive substrates of OATP1B1/3, OAT1, OCT1, OCT2, MATE1 and P-gp are prohibited. If medically feasible, patients taking regular medication, with the exception of examples of known substrates of transporters listed in Table 25, should be maintained on it throughout the study period.

Table 25 Examples of Substrates of Transporters

Substrate category	Examples of drugs in the category
Substrates of:	
BCRP	methotrexate, mitoxantrone, imatinib, lapatinib, sulfasalazine, topotecan, daunorubicin, doxorubicin, SN-38, irinotecan, prazosin, pantoprazole, atorvastatin, fluvastatin, rosuvastatin, and simvastatin.
OAT1	adefovir, captopril, furosemide, lamivudine, methotrexate, oseltamivir, tenofovir, zalcitabine, zidovudine, ciprofloxacin, cephaloridine, methotrexate, pravastatin
OATP1B1, OATP1B3	asunaprevir, atorvastatin, bosentan, danoprevir, docetaxel, fexofenadine, glyburide, nateglinide, paclitaxel, pitavastatin, pravastatin, repaglinide, rosuvastatin, simvastatin acid
OCT1	metformin, oxaliplatin, aciclovir, ganciclovir
OCT2	metformin, pindolol, procainamide, ranitidine amantadine, amiloride, oxaliplatin, varenicline, cisplastin, debrisoquine, propranolol, guanidine, D-tubocurarine, pancuronium, memantine, picoplatin, ifosfamide, cimetidine, famotidine, zalcitabine, lamivudine, berberine
MATE1	metformin
P-gp	dabigatran etexilate, digoxin, fexofenadine

Herbal Preparations

Herbal preparations/medications are not allowed throughout the study, starting 7 days prior to first dose of AZD4635. These herbal medications include but are not limited to St. John's wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng.

Prohibited medications with Cabazitaxel

Avoid concomitant administration of strong CYP3A4 inhibitors/inducers (see Table 26) with cabazitaxel administration (Arm B). In addition, live attenuated vaccines should not be given through 3 months after the last dose of cabazitaxel.

Table 26 Examples of Strong CYP3A4 Inducers and Inhibitors

	Examples of drugs in the category
CYP3A4 inducers	phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, St. John's wort
CYP3A4 inhibitors	ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole

Table 27 Prohibited Medications with Durvalumab

Prohibited medication/class of drug:	Additional information
mAbs against CTLA-4, PD-1, or PD-L1 other than those under investigation in this study	Should not be given concomitantly while the participant is on study intervention
Live attenuated vaccines	Should not be given through 30 days after the last dose of durvalumab
Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumour necrosis factor-α blockers	Should not be given concomitantly, or used for premedication prior to the I-O infusions. The following are allowed exceptions: Use of immunosuppressive medications for the management of IP-related AEs Use in participants with contrast allergies. In addition, use of inhaled, topical, and intranasal corticosteroids is permitted. A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of non-immunotherapy related events experienced by the participant (e.g., chronic obstructive pulmonary disease, radiation, nausea, etc.).
Epithelial growth factor receptor tyrosine kinase inhibitors (EGFR TKIs)	Should not be given concomitantly. Should be used with caution in the 90 days post-last dose of durvalumab. Increased incidences of pneumonitis (with third generation EGFR TKIs) and increased incidence of transaminase increases (with first-generation EGFR TKIs) has been reported when durvalumab has been given concomitantly.

Appendix J Brief Pain Inventory (short form) Example – Not for Participant Use

1903

Date: ☐☐ / ☐☐ / ☐☐
(month) (day) (year)

Subject's Initials : _____

Study Subject #: ☐☐☐☐

PLEASE USE BLACK INK PEN

Study Name: _____

Protocol #: _____

PI: _____

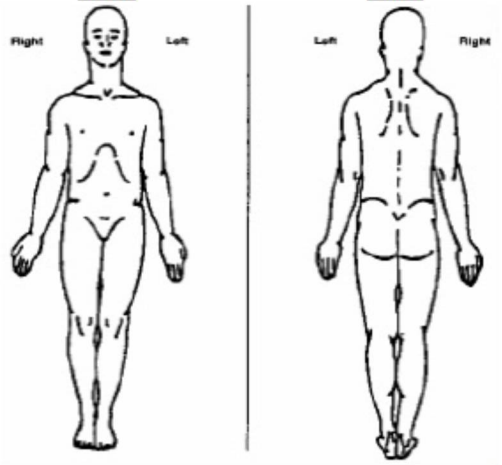
Revision: 07/01/05

Brief Pain Inventory (Short Form)

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

☐ Yes ☐ No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by marking the box beside the number that best describes your pain at its worst in the last 24 hours.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
No Pain — Pain As Bad As You Can Imagine

4. Please rate your pain by marking the box beside the number that best describes your pain at its least in the last 24 hours.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
No Pain — Pain As Bad As You Can Imagine

5. Please rate your pain by marking the box beside the number that best describes your pain on the average.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
No Pain — Pain As Bad As You Can Imagine

6. Please rate your pain by marking the box beside the number that tells how much pain you have right now.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
No Pain — Pain As Bad As You Can Imagine

Page 1 of 2

1903

Date: (month) / (day) / (year)

Subject's Initials : _____

Study Subject #:

PLEASE USE BLACK INK PEN

Study Name: _____

Protocol #: _____

PI: _____

Revision: 07/01/05

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please mark the box below the percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
☐ No Relief	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐ Complete Relief

9. Mark the box beside the number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
Does Not Interfere										Completely Interferes

B. Mood

☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
Does Not Interfere										Completely Interferes

C. Walking ability

☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
Does Not Interfere										Completely Interferes

D. Normal Work (includes both work outside the home and housework)

☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
Does Not Interfere										Completely Interferes

E. Relations with other people

☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
Does Not Interfere										Completely Interferes

F. Sleep

☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
Does Not Interfere										Completely Interferes

G. Enjoyment of life

☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
Does Not Interfere										Completely Interferes

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Appendix K FACT-P (Version 4) Example - Not for Participant Use

FACT-P (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

English (Universal)

19 November 2007
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FACT-P (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-P (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
C2	I am losing weight	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
P1	I have aches and pains that bother me	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
P3	My pain keeps me from doing things I want to do	0	1	2	3	4
P4	I am satisfied with my present comfort level	0	1	2	3	4
P5	I am able to feel like a man	0	1	2	3	4
P6	I have trouble moving my bowels	0	1	2	3	4
P7	I have difficulty urinating	0	1	2	3	4
BL2	I urinate more frequently than usual	0	1	2	3	4
P8	My problems with urinating limit my activities	0	1	2	3	4
BL5	I am able to have and maintain an erection	0	1	2	3	4

Appendix L COVID-19 Specifics

L 1 Background to COVID-19

There is currently an outbreak of respiratory disease (COVID-19) caused by a novel SARS-CoV-2 that was first detected in Wuhan City, Hubei Province, China in 2019. This new virus has rapidly spread across the globe causing the WHO to declare a pandemic situation on 12 March 2020. The countermeasures initiated by national and local governments worldwide and the recommendations issued by the health authorities have impacted current and new clinical studies. As the threat of pandemic burden including new outbreaks, locally or globally, will impact the further conduct of clinical studies, appropriate risk assessments and mitigation measures will need to be taken into consideration in all clinical studies to protect participants, site staff, and society as a whole.

Both EMA and FDA as well as national health authorities in Europe have issued new guidelines that aim to provide recommendations for actions for conduct of clinical studies of medical products during COVID-19 pandemic. Since the pandemic situation is evolving, guidelines, recommendations, national laws, and local restrictions may change at high pace. Given the circumstances of potentially relapsing pandemic or epidemic situation with regard to the spread of COVID-19 in future, special attention will be paid to protect participants participating in the study and site staff involved in the investigations against infection with SARS-CoV-2 as requested by the newly issued EMA guideline.

L 2 Risk Assessment in view of the COVID-19 Pandemic

There are 3 study drugs with different mechanisms of action that are unlikely to impact on the course of infection with SARS-CoV-2.

It is possible that respiratory symptoms of pneumonitis could arise due to durvalumab or cabazitaxel that may be difficult to distinguish clinically from COVID-19. It is recommended that evaluation be done including imaging and infectious disease testing to try to understand the causality of such events to the extent that is possible.

AZD4635 alone has not resulted in significant immune-mediated toxicity although close monitoring will be done including monitoring of adverse events. It is not anticipated that AZD4635 should worsen infection with COVID-19 but there is no clinical data available at this time.

Durvalumab therapy may lead to AEs including, 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. Adverse events of special interest (AESIs) for durvalumab also include pneumonitis. It is possible, albeit rare, that events with an inflammatory or immune-mediated

mechanism could occur in nearly all organs.

While, this poses a theoretical risk of adversely influencing the antiviral response, this is judged to be unlikely. Therefore, risk of the participants exposed to SARS-CoV-2 or to suffer from COVID-19 is expected to be similar to the background population with the same co-morbidities as those in the study. The risk of exposure to infected people cannot be completely excluded as the participants may need to expose themselves to public areas (e.g., commute to the site) and have additional human contact (eg, with site staff and other participants of the clinical study).

Measures to mitigate the additional risks caused by COVID-19 are:

- This study is going to start enrolling only when the Sponsor and CRO in collaboration deem it is safe to start the study. In addition, the study will not start until the local confinement measures or other safety restrictions linked to the COVID-19 pandemic imposed by the local authorities are compatible with safe conduct of the study. Current national laws and local recommendations for prevention of pandemic will be strictly adhered to.

- During the study, COVID-19 tests may be prescribed, if required, and in accordance with local guidance. If a participant tests positive, his continued participation in the study and his treatment with the study drugs will be discussed with the Parexel and AstraZeneca Medical Monitors for this study.

- The probability of virus transmission will be controlled as much as possible by:

    - Advice for participant to adhere to local requirements for reduction of the public exposure while ambulatory.

    - Confirmation of COVID-19 infection by optional laboratory assessment will be conducted based on availability (test capacity and turnaround time) of approved tests and on Investigator's discretion. If applicable, participants will be referred to the local health care system for further follow-up and treatment.

    - Physical distancing and person-to-person contact restrictions will be applied during site visits and in-house confinement.

    - Where physical distancing is not possible, PPE will be used by study participants (surgical face mask, gloves) and staff (for example but not limited to masks, gloves, protectors, medical suits) if deemed appropriate by the Investigators and site staff and guided by local requirements.

    - Logistical improvements of the site and structural measures of the study site

building will be implemented to further improve physical distancing.

- Home or remote visit to replace on-site visit (where applicable): A qualified Health Care Professional (HCP) from the study site or third-party vendor service may visit the patient's home or other remote location as per local standard operating procedures, as applicable. Supplies will be provided for a safe and efficient visit. The qualified HCP will be expected to collect information per the Clinical Study.

- Telemedicine visit to replace on-site visit (where applicable): In this Appendix, the term telemedicine visit refers to remote contact with the patients using telecommunications technology including phone calls, virtual or video visits, and mobile health devices. During a civil crisis, natural disaster, or public health crisis, on-site visits may be replaced by a telemedicine visit if allowed by local/regional guidelines. Having a telemedicine contact with the patients will allow AEs, concomitant medication, patient report outcomes questionnaires, and health economic data to be reported and documented.

- Remote location Investigational Product administration instructions: If a site visit is not possible, administration of Investigational Product may be performed at a remote location by a qualified HCP from the study site or third party vendor service (eg, infusion centers, external non-hospital medical settings, alternate clinical site locations), if appropriate per local regulatory requirements. The remote location must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit participants to an intensive care unit if necessary. The option of Investigational Product administration at a remote location ensures patient's safety in cases of a pandemic where patients may be at increased risk by traveling to the site/clinic. This will also minimize interruption of Investigational Product administration during other study disruptions, e.g., site closures due to natural disaster.

    - Investigational Product administration at a remote location: Prior to remote location Investigational Product administration, the investigator must confirm whether administration of Investigational Product at the considered remote location is appropriate for the participant. All necessary supplies and instructions for administration and documentation of Investigational Product administration will be provided. More information related to the visit can be obtained via a telemedicine or home/remote visit.

L 3 Restrictions Related to COVID-19

During the COVID-19 pandemic, participants are advised to adhere to local requirements for reduction of the public SARS-CoV-2 exposure while ambulatory. If appropriate, participants will be referred to the local health care system. Physical distancing and person-to-person contact restrictions will be applied and explained to participants while staying at the study site. Where physical distancing is not possible, study participants will be asked to use surgical face masks and/or gloves if deemed appropriate by the Investigator and site staff and guided by local requirements.

L 4 Data Quality Assurance Related to COVID-19

Monitoring visits at site will be limited to a minimum required as deemed appropriate during COVID-19 pandemic, per local regulations. All AEs/SAEs should be reported in line with instructions for safety reporting documented in the CSP. For patients experiencing signs and symptoms indicating an infection, an attempt will be made to determine whether the COVID-19 virus is the infectious organism and the AE will be recorded accordingly. If COVID test results are available to the site staff, they will be recorded as either “COVID-19 positive” or “COVID-19 negative” in the Adverse Event Field, along with the AE/SAE signs and symptoms and/or other diagnosis.

If a test has not been performed or result is not available and signs and symptoms, as judged by the Investigator, are highly suggestive of COVID-19 infection, record “COVID-19 suspected” in the Adverse Event Field. If the Investigator has other concurrent diagnoses for the patient’s signs and symptoms (eg, pneumonia), these will be recorded as separate AEs.

In addition, where possible, other measures for carrying out protocol related activities, such as but not limited to home nursing, may be employed as required. Data collected during telemedicine or home/remote visits will be captured by the qualified HCP from the study site or third-party vendor service in the source documents, or by the patient themselves.

L 5 References

1. Guidance on the Management of Clinical Trials during the COVID 19 (Coronavirus) pandemic, EMA, Version 3 (28/04/2020). https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf.

2. FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency, March 2020, Updated on April 16, 2020 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fdaguidance-conduct-clinical-trials-medical-products-during-covid-19-public-healthemergency.

Appendix M Abbreviations

Abbreviation or special term	Explanation
$A_{2A}R$	Adenosine 2A receptor
AARDVARC	**$A_{2A}R$ inhibitor and DurValumab Assessment of Response in CRPC**
ADA	Adenosine deaminase
ADO	Adenosine
AE	Adverse event (see definition in Appendix B)
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BID	Twice daily
BPI-SF	Brief Pain Inventory (Short Form)
CD73	Cluster of differentiation 73: 5'-nucleotidase (5'-NT) or ecto-5'-nucleotidase
CI	Confidence interval
CL	Clearance
CL/F	Apparent plasma clearance
C_{max}	Maximum observed concentration
CNS	Central nervous system
COVID-19	Coronavirus disease of 2019
CR	Complete response
CRC	Colorectal carcinoma
CSP	Clinical study protocol
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CCI	[redacted]
CYP	Cytochrome P450
DCO	Data cut-off
DDI	Drug-drug interaction
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
eCRF	Electronic case report form
ES-SCLC	Extensive-stage small cell lung cancer

Abbreviation or special term	Explanation
FACT-P	Functional Assessment of Cancer Therapy-Prostate
FDA	Food and Drug Administration
G-CSF	Granulocyte-colony stimulating factor
GCP	Good Clinical Practice
GGT	Gamma-glutamyltransferase
GLP	Good Laboratory Practice
GRH	Gonadotropin-releasing hormone
IATA	International Air Transport Association
IB	Investigator's Brochure
IC_{50}	Concentration giving 50% of the drug-induced inhibitory effect
ICF	Informed consent form
ICH	International Council for Harmonisation
IFNγ	Interferon gamma
Ig	Immunoglobulin
IHC	Immunohistochemistry
ILD	Interstitial lung disease
imAE	Immune-mediated adverse events
IMP	Investigational medicinal product
IO	Immunotherapy
IP	Investigational product
IRB	Institutional Review Board
IV	Intravenous
mAb	Monoclonal antibody
mCRPC	Metastatic castrate-resistant prostate carcinoma
MedDRA	Medical Dictionary for Regulatory Activities
MOA	Mechanism of action
MRI	Magnetic resonance imaging
CCI	[redacted]
MTD	Maximum-tolerated dose
MUGA	Multiple-gated acquisition
nAb	Neutralizing antibody
NE	Not evaluable
NHA	New hormonal agent(s)
NIMP	Non-investigational medicinal product
NK	Natural killer (cells)

Abbreviation or special term	Explanation
NOAEL	No-observed-adverse-effect level
NTL	Non-target lesion
OAE	Other significant adverse event
ORR	Objective response rate
OS	Overall survival
CCI	[redacted]
PD	Progression of disease
PD-1	Programmed cell death protein 1 (e.g., nivolumab [Opdivo®])
PD-L1	Programmed death ligand 1
PET	Positron emission tomography
PI	Prescribing information
PK	Pharmacokinetics
PO	*Per os* (orally)
PR	Partial response
PRO	Patient reported outcome
PRED	Prednisone
PSA	Prostate-specific antigen
Q3W	Every 3 weeks
Q4W	Every 4 weeks
QD	Once daily
QT	ECG interval measured from the onset of the QRS complex to the end of the T wave
QTc	QT interval corrected for heart rate
QtcF	QT interval corrected for heart rate using Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumours
rPFS	Radiographic progression-free survival
SAE	Serious adverse event (see definition in Section 8.3)
SCCHN	Squamous cell carcinoma head and neck
SD	Stable disease
SoA	Schedule of activities
SRC	Safety Review Committee
STD_{10}	$1/10^{th}$ of the severely toxic dose in rodent studies
SmPC	Summary of Product Characteristics
TBNK	Complete immune panel (T-, B-, and NK lymphocyte subsets)
CCI	[redacted]
TEAE	Treatment-emergent adverse event

Abbreviation or special term	Explanation
TID	Three times a day
TL	Target lesion
t_{max}	Time to reach C_{max}
TME	Tumour microenvironment
TMGs	Toxicity Management Guidelines
TNα	Tumour necrosis factor-α
TNBC	Triple-negative breast cancer
Treg	Regulatory T cells
ULN	Upper limit of normal
USPI	United States Prescribing Information
WHO	World health organisation (performance status)

Appendix N Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

Amendment 1, 07-September-2020

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the council of the European Union.

Overall Rationale for the Amendment:

The global protocol was amended to address comments received from various health authorities in the EU. A summary of changes and the rationale for each change are tabulated below.

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
1.1 Synopsis and 2.1 Study Rationale	Edited with updated data from AZD4635 Investigator's Brochure (IB) Ed 6.1, dated 12 Aug 2020	Information from new data cut-off date (02 Dec 2019) was available	Substantial
1.1 Synopsis and 3 Objectives and Endpoints	The list of parameters for which laboratory values will be recorded to evaluate safety of each treatment regimen was clarified	Added to the endpoints column for clarity	Non-substantial
1.1 Synopsis and 3 Objectives and Endpoints	It was clarified that the Pharmacokinetic (PK) parameters for the study drugs will be derived, where deemed appropriate.	Added to clarify that derived PK parameters for all study drugs may be presented, only where deemed appropriate – given the sparse and intense PK sampling.	Non-substantial
1.1 Synopsis and 3 Objectives and Endpoints	The following was added to the objectives and endpoints table "Time to pain progression based on BPI-SF Item 3 'pain at its worst in the last 24 hours' will be additionally summarised for the high and low gene expression subgroups for ADO and ADA in each arm separately.	Added per input from study team.	Substantial
1.1 Synopsis and 3 Objectives and Endpoints	The secondary objective "To explore the effects of AZD4635 on pain and other prostate cancer-related symptoms." was edited to "To **determine** the effects….".	Edited to ensure that it is not perceived as an exploratory objective	Non-substantial
1.1 Synopsis and 3 Objectives and Endpoints 8.2.9 Clinical outcome assessments	Endpoint for the secondary objective "To determine the effects of AZD4635 on pain and other prostate cancer-related symptoms." was edited to clarify that change from baseline in average pain would be recorded instead of general pain, and that time to pain progression based on Item 3 - "pain at its worst in the last 24 hours" - of the Brief Pain Inventory (Short Form) (BPI-SF) would be measured. The worst bone pain item of the BPI-SF was omitted.	Revised per input from study team.	Substantial
1.1 Synopsis, 3 Objectives and Endpoints, and 8.2.9 Clinical outcome measures	Endpoint for the secondary objective "To determine the effects of AZD4635 on pain and other prostate cancer-related symptoms." was edited to add "FAPSI–6 as derived from 6 items" of the Functional Assessment of Cancer Therapy-Prostate (FACT-P) scale. FACT Advanced Prostate Symptom Index-6 (FAPSI-6) was also added to the clinical outcome measures under FACT-P, in Section 8.2.9 Clinical	Revised per input from study team.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
	outcome measures. FAPSI-6 is a subset of FAPSI-8 which was already in the protocol.		
1.1 Synopsis, 2 Introduction, and 4.1 Overall design	The following instruction was added: Participants in Arm B will receive cabazitaxel chemotherapy as per the local label. This will start approximately 1 hour (or up to a maximum of 2 hours) after the end of the durvalumab infusion. Cabazitaxel will be administered as per the local prescribing guidelines for a maximum of 10 cycles. After cycle 10 durvalumab + AZD4635 will be administered Q4W to harmonise with the Arm A treatment cycle length.	Revised per input from study team.	Substantial
1.1 Synopsis and 4.1 Overall Design	During the study, tests for active Coronavirus disease of 2019 (COVID-19) infection may be conducted, if required, and in accordance with local guidance. In the overall design section, it was further clarified that "If a participant is symptomatic for active COVID-19 infection during a site visit, he may be prescribed a COVID-19 test. Dosing may continue while results are awaited, per the Investigator's discretion and local guidelines, and the Medical Monitor/AstraZeneca Study Physician should be consulted. For participants who test positive (for COVID-19) the study drugs may be temporarily interrupted and later resumed, per the Investigator's discretion and local guidelines, and this should be discussed with the Medical Monitor/AstraZeneca Study Physician. Where applicable, home or remote visits may be conducted for study assessments and study drug administration (see Appendix L)."	Added in view of ongoing COVID-19 pandemic	Substantial
1.1 Synopsis and 6 Study intervention	The following statement was added: In this protocol AZD4635, durvalumab and cabazitaxel are all referred to as either study drugs, study interventions, investigational products, or investigational medicinal products, and these terms are used interchangeably.	Revised to add clarity regarding terminology used in protocol	Non-substantial
1.1 Synopsis and 9.5 Interim analysis	The term "Bayesian predictive probability" was changed to "predictive probability". It was also clarified that participant recruitment will	Revised per input from study team.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
	continue while the interim analysis is ongoing, but may be paused if the number of participants in Arm A reaches approximately 50.		
1.3 Schedule of Activities	Visit windows for the follow-up visits were clarified in the header for Tables 1 and 2 and a footnote is added to describe the timing of the first progression-free follow-up	Revised for clarity	Non-substantial
1.3 Schedule of Activities	New activities added to both Tables 1 and 2 for Echocardiogram (ECG)/multiple-gated acquisition (MUGA) assessment at screening. Relevant footnotes have also been added to indicate additional assessments for echocardiogram/MUGA during the study.	Regulatory request to add echocardiogram/MUGA assessment at screening in order to exclude participants with ejection fraction < 55%.	Substantial
1.3 Schedule of Activities	New activities added to both Tables 1 and 2 to allow for a test for COVID-19, if required. A relevant footnote was also added to clarify that "During the study, tests for active COVID-19 infection may be prescribed, if required, and in accordance with local guidelines."	Added in view of ongoing COVID-19 pandemic	Substantial
1.3 Schedule of Activities and 8.2.6 Concomitant medications	It was clarified in both Tables 1 and 2 that concomitant medications at the 90-day follow-up and progression-free follow-up visits would only be to gather data on cancer therapy. Section 8.2.6 was also updated accordingly.	Revised per study team input to capture subsequent cancer therapy	Substantial
1.3 Schedule of Activities	It as clarified in both Tables 1 and 2 that Adenosine (ADO) biomarker assessments were "ADO signalling gene expression". This was also cascaded in the protocol.	Revised per study team input	Non-substantial
CCI [redacted]	[redacted]	[redacted]	[redacted]
1.3 Schedule of Activities	New activity added to Table 2 for cabazitaxel post-dose PK sampling, and timepoints for AZD4635 and durvalumab sampling were edited	These edits were made for consistency with	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
		planned analyses in protocol body.	
1.3 Schedule of Activities	Imaging efficacy assessments were edited to add positron emission tomography (PET) scans to tumour imaging per Response Evaluation Criteria in Solid Tumours (RECIST) criteria, and to add a ±1 week visit window during the treatment period in both Tables 1 and 2 for consistency with elsewhere in the protocol.	Revised per study team input	Substantial
1.3 Schedule of Activities	Footnotes were added to each, Tables 1 and 2, allowing that routine clinical and safety assessments may be done 1 day prior to each visit, if required, and that the patient reported outcome (PRO) instruments will be administered and completed at the start of each visit.	Revised per study team input	Substantial
CCI [redacted]	[redacted]	[redacted]	[redacted]
1.3 Schedule of Activities	A footnote was added to Table 2, with reference to the haematology assessment, to confirm that the haematology assessment will include full blood count	Regulatory request to include full blood count at Week 2 as weekly measurements are recommended during Cycle 1 for cabazitaxel.	Substantial
1.3 Schedule of Activities	A footnote was added to Table 2, to provide reference to Section 6.7.3 and Table 12 which includes instruction on hypersensitivity monitoring during cabazitaxel infusion, and dose modifications in the event of toxicities.	Revised per study team input	Non-substantial
1.3 Schedule of Activities	For Tables 1 and 2, the Scheduled assessments for ePROs were updated to make consistent with protocol body and statistical analysis plan (SAP).	Revised per update to SAP and per study team input	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
2 Introduction, 4.3 Justification of dose, and 6.2.3 Cabazitaxel	Added the United States (US) prescribing information as one of the reference safety documents for cabazitaxel.	Revised per study team input	Substantial
2.2 Background	Extensive-stage small cell lung cancer (ES-SCLC) was added to the durvalumab indications in the US.	Updated per March 2020 update to the US prescribing information	Non-substantial
2.2.1 Benefit/risk Assessment	This section was updated with an updated data-cut-off of 02 December 2019.	Revised with new data available in the IB	Substantial
2.2.1 Benefit/risk Assessment	This section was updated to include a link to Appendix L describing risk considerations for COVID-19.	Added in view of ongoing COVID-19 pandemic	Substantial
3 Objectives and endpoints	CCI [redacted]	Revised per study team input	Non-substantial
3 Objectives and endpoints	CCI [redacted]	Revised for clarity per study team input	Substantial
4.1.1 Safety Review Committee	It was clarified that the study team will consider halting recruitment **at any point** during the Safety Review Committee (SRC)'s review, until full analysis and review by the SRC is available.	Revised for clarity regarding participant recruitment during SRC review per study team input	Substantial
5.1. Inclusion Criteria and 8.3.9.1 Paternal exposure	Inclusion criterion number 7 updated to replace "barrier methods" with "male condom" and to extend contraception requirement to **6 months** after last dose of cabazitaxel.	Regulatory request to update as the cabazitaxel Summary of Product Characteristics (SmPC) observes that exposure of another person to study	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
		drug via ejaculate must be prevented.	
5.1. Inclusion Criteria and 8.3.9.1 Paternal exposure	The timeline for reporting of the outcome of a pregnancy for a female partner of a participant was updated in Section 8.3.9.1 (Pregnancy): "However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring any time from the first date of dosing for AZD4635, durvalumab and cabazitaxel until 3 months (Arm A) or 6 months (Arm B) after the last dose of the study drugs should, if possible, be followed up and documented until 30 days after birth. As deemed appropriate, the pregnancies will be followed up per local guidance and regulatory requirements." A reference to Section 8.3.9.1 was added to inclusion criterion 7 in Section 5.1	Updated per input from ethics committees	Substantial
5.1. Inclusion Criteria	Update of inclusion criterion 8 to clarify the haemoglobin level for Arm B: "Haemoglobin ≥9.0 g/dL **(≥10.0 g/dL for Arm B)**"	Regulatory request to be accordance with the SmPC of cabazitaxel.	Substantial
5.1 Inclusion criteria	Update of inclusion criterion 10 to add that "Patients who were eligible for both Arm A and Arm B will be preferentially allocated to Arm B, until enrollment of Arm B is completed."	Revised for clarity per study team input	Substantial
5.2. Exclusion Criteria	Exclusion criterion number 2 has been expanded to include: **For current or prior use of immunosuppressive medication within 14 days before the first dose the following will be exceptions to this:** **Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra-articular injection)** **Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent** **Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication)**	Regulatory request to expand this exclusion criterion to account for the immune system profiles of the study drugs.	Substantial
5.2. Exclusion Criteria	Exclusion criterion number 3 was updated to delete the text "requiring corticosteroids":	Regulatory request to update since more than	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
	Participant with a history of pneumonitis ~~requiring corticosteroids~~.	one study drug in this study may cause pneumonitis and the risk in combination therapy to participants with any history of pneumonitis without qualification is therefore sufficient to exclude the participant.	
5.2. Exclusion Criteria	Exclusion criterion number 5 has been expanded to include additional systemic diseases that would require exclusion from the study. "As judged by the Investigator, any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension, active bleeding diatheses, active infection including hepatitis B, hepatitis C, and human immunodeficiency virus, **chronic gastrointestinal diseases (eg, Crohn's disease, chronic colitis), ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, uncontrolled cardiac arrhythmia, or active interstitial lung disease (ILD).**"	Regulatory request to expand this exclusion criterion to account for information in the AZD4635 IB (chronic gastrointestinal diseases) and toxicity profiles of the study drugs.	Substantial
5.2. Exclusion Criteria	Addition of exclusion criteria numbers 8, 9, and 10: **8. History of allogeneic organ transplantation.** **9. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [eg, colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], 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 (eg, following Hashimoto syndrome) stable on hormone replacement** **Any chronic skin condition that does not require systemic therapy**	Regulatory request to add these exclusion criteria since the study drugs modify the immune system.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
	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** **10. History of active primary immunodeficiency.**		
5.2. Exclusion Criteria	Addition of exclusion criterion number 11: **Active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and tuberculosis testing in line with local practice).**	Regulatory request to include since the durvalumab SmPC specifies that participants with tuberculosis were excluded from clinical trials of durvalumab, the clinical implications in this study of combination therapies are unknown, and therefore, participants with tuberculosis need to be specified as excluded.	Substantial
5.2. Exclusion Criteria	Previous exclusion criterion number 16 has been moved up to exclusion criterion 12	Exclusion criterion for vaccines should be included for all participants and not just for those in Arm B.	Substantial
5.2. Exclusion Criteria	Update of exclusion criterion number 16 to clarify hypersensitivity to study drugs and excipients: "History of hypersensitivity **to any of the study drugs or any of the study drug excipients including hypersensitivity** to polysorbate-80 if allocated to cabazitaxel."	Regulatory request to update the criterion to specify hypersensitivity to all study drugs and study drug excipients.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
5.2. Exclusion Criteria and 6.5 concomitant medication	Exclusion criteria 18, 19 and 20, and the concomitant medication section, were updated to include updated instruction for disallowed medication.	Revised per study team input	Substantial
5.2. Exclusion Criteria	Exclusion criterion 25 was updated with detail "History of allogeneic **organ, or other transplant, such as bone marrow transplant**	Revised per study team input	Substantial
5.2. Exclusion Criteria	A correction was made to exclusion criterion 28 to exclude participants with concomitant treatment with another adenosine 1 receptor (**A_1R**) antagonist	Revised per study team input	Substantial
5.2 Exclusion criteria	Clarity was added to exclusion criterion 29 regarding cardiac criteria: Ejection fraction <55% or the lower limit of normal of the institutional standard, **ascertained by an echocardiogram or MUGA that has been obtained in the 6 months prior to screening. If there has been a change in the participant's cardiac status, or if there has not be an echocardiogram or MUGA within the 6 months prior to study enrollment, this should be performed as part of the screening assessments**	Revised per study team input	Substantial
5.3.1 Meals and dietary restrictions	Dietary restrictions for participants in Arm B were clarified	Revised per study team input	Substantial
6.1.1 Investigational products	Text regarding packaging and labelling was revised	Revised per input from clinical logistics team	Non-substantial
6.2.1 AZD4635	Broadened language that states that AZD4635 can be taken with food.	Revised per input from study team	Non-substantial
6.5.2. Prohibited or Restricted Medications	Addition of a new sub-heading "**Prohibited or Restricted Medications**"	Regulatory request to clarify appropriate sub-heading to match the contents of text and Tables 5, 6, 7, and 8.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
6.5.3 Drug-drug interactions	Drug-drug interactions with AZD4635 were updated	Revised per updated IB Version 6.1, dated 12 Aug 2020	Substantial
6.6.1. Definition of Dose-Limiting Toxicity for Arm B	Text has been added to clarify haematological dose limiting toxicities as below: "**Haematological toxicities CTCAE ≥ Grade 3 not attributed to cabazitaxel alone, except for neutropenia, which is addressed as:** Neutropenia ≥ CTCAE Grade 4 or febrile neutropenia present for more than 7 days. For AZD4635/cabazitaxel/durvalumab it will not be considered a DLT if attributed to cabazitaxel only."	Regulatory request to update to specify "haematological toxicities…" as the text was limited to one specified event suggesting that every other significant haematological toxicity is excluded from consideration as drug-limiting toxicity (DLT).	Non-substantial
6.7.2 Management of Toxicities Related to Durvalumab Therapy	The following text was deleted, as it is not intended, and for consistency with the rest of the protocol: "~~If medically appropriate, dose modifications are permitted after discussion with the Medical Monitor/AZ Study Physician. All dose modifications should be documented with clear reasoning and documentation of the approach taken~~."	Revised per input from study team	Substantial
6.7.2.1. Specific Toxicity Management Guidelines and Dose Modification Information for Durvalumab	Clarification was provided that specific toxicity management guidelines and dose modification information is for durvalumab and so "tremelimumab" has been deleted from the text pertaining to the guidelines. All related text deleted. Also, the following hyperlink was deleted as it was not active:	Regulatory request to remove description of tremelimumab as it is not a study drug for this study. Regulatory request to check inactive hyperlink.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
	"~~In addition, a current version of TMGs is available through the following link: https://tmg.azirae.com. Please contact the clinical study associate for information on how to gain access to this website~~"		
6.7.2.1. Specific Toxicity Management Guidelines and Dose Modification Information for Durvalumab	Addition of text to clarify the risks associated with durvalumab: **"Risks with durvalumab include, but are not limited to, diarrhoea/colitis, pneumonitis/ILD, endocrinopathies (i.e., events of hypophysitis/hypopituitarism, adrenal insufficiency, hyper- and hypo-thyroidism, type I diabetes mellitus and diabetes insipidus), hepatitis/increases in transaminases, nephritis/increases in creatinine, rash/dermatitis, myocarditis, myositis/polymyositis, infusion-related reactions, hypersensitivity reactions, pancreatitis, serious infections, and other rare or less frequent inflammatory events including neuromuscular toxicities (e.g. Guillain-Barre syndrome, myasthenia gravis)"**	Regulatory request to indicate toxicities for durvalumab.	Substantial
6.7.3. Management of Toxicities Related to Cabazitaxel Therapy	Addition of peripheral neuropathy dose modification actions to Table 12.	Regulatory request to add neurological toxicity and potential dose modifications.	Substantial
6.7.3. Management of Toxicities Related to Cabazitaxel Therapy	Addition of text to describe close monitoring for hypersensitivity reactions: "**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. Severe reactions can occur and may include generalised rash/erythema, hypotension and bronchospasm. Severe hypersensitivity reactions require immediate discontinuation of cabazitaxel and appropriate therapy.**"	Regulatory request to include close monitoring as indicated in the cabazitaxel SmPC for the first and second infusions due to the risk of hypersensitivity reactions.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
7.2 Participant withdrawal from the study	Text was added to provide guidance: "During the study, COVID-19 tests may be prescribed, if required, and in accordance with local guidance. If a participant tests positive, his continued participation in the study and his treatment with the study drugs will be discussed with the Parexel and AstraZeneca Medical Monitors for this study."	Added in view of ongoing COVID-19 pandemic	Substantial
8.1.2 PCWG3 Bone Lesion Assessment	PET scan was removed from this section as it is not intended for this assessment	Revised per study team input	Substantial
8.2.1. Physical Examinations and Weight	Physical examination description has been updated to clarify that: "**Physical examinations will include assessments of the head, eyes, ears, nose, and throat and the respiratory, cardiovascular, gastrointestinal, urogenital, musculoskeletal, neurological, dermatological, hematologic/lymphatic, and endocrine systems. Height will be measured at screening only.**"	Regulatory request to add neurological examination to remind Investigators of the importance of neuropathic toxicity with durvalumab and cabazitaxel.	Non-substantial
8.2.4 Electrocardiograms	The reference to study specific ECG manual was deleted as routine evaluation of the ECGs is intended	Revised per study team input	Substantial
8.2.5. Echocardiogram/MUGA	New section has been included to describe echocardiogram/MUGA requirements.	A new section for echocardiogram/MUGA has been added since echocardiogram/MUGA assessments have been included in the schedule of activities.	Substantial
8.2.8 Other assessments	New section added and additional text added to clarify that the prostate-specific antigen (PSA) CCI samples will be analysed by a local laboratory and a central laboratory, respectively	Revised per study team input	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
8.2.8 Other assessments	Text was added to provide guidance around COVID-19 testing in the study: "**COVID-19 testing** During the study, tests for active COVID-19 infection may be prescribed, where appropriate, and in accordance with local procedures. If a participant tests positive, his continued participation in the study and his treatment with the study drugs will be discussed with the Parexel and AstraZeneca Medical Monitors for this study."	Added in view of ongoing COVID-19 pandemic	Substantial
8.2.9 Clinical outcome measures	Revised to clarify that the PRO questionnaires should be completed at the start of each visit.	Revised per study team input	Non-substantial
8.2.10 Survival follow-up	The following text was added "Note: when required 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 after the DCO date these participants will be censored at the date of DCO. When required 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."	Revised per study team input	Non-substantial
8.3.3 Causality collection	It was clarified that AZD4635, durvalumab and cabazitaxel are all investigational products that will be considered for causality assessment	Revised for clarity per study team input	Substantial
8.3.9.1. Paternal Exposure	Addition of text regarding the storage of sperm in Arm B: "**Participants in Arm B will be advised on storage of sperm prior to receiving cabazitaxel due to the possibility of irreversible infertility/testicular damage due to cabazitaxel therapy.**"	Regulatory request to instruct Investigators to provide advice to participants on the conservation of sperm	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
		prior to treatment because of the possibility of irreversible infertility/testicular damage due to therapy with cabazitaxel as noted in SmPC.	
8.3.9.1. Paternal Exposure	The period for follow-up of pregnancy outcomes was clarified for each treatment arm: "However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring any time from the first date of dosing for AZD4635, durvalumab and cabazitaxel until 3 months (Arm A) or 6 months (Arm B) after the last dose of the study drugs should, if possible, be followed up and documented until 30 days after birth. As deemed appropriate, the pregnancies will be followed up per local guidance and regulatory requirements"	Revised for clarity, per team input	Substantial
8.4 Overdose	Text in this section was rephrased to clarify that "If associated with an AE, any dose in excess of the dose specified according to the protocol will constitute an overdose."	Revised for clarity, per team input	Non-substantial
8.5.1 Pharmacokinetics	This section was updated to provide clarity on the schedule for PK assessments, and to add a note to Table 17 that **The SRC will review the data from the first 6 evaluable participants receiving Cycle 1 of Arm B and if agreed after the data review subsequent participants entering the study will follow the PK sampling schedule in Table 18. Recruitment in Arm B may continue until the SRC complete their review and their decision is made. Intense PK sampling per Table 17 may be performed for > 6 participants until the SRC decision is made**	Revised for flexibility and clarity, per team input	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
8.5.1. Pharmacokinetics, Table 19	Text added as footnote to Table 19 to clarify that the first 6 participants in Arm B will have cabazitaxel PK samples collected during Cycle 1.	Clarification that PK data is required from only the first 6 participants.	Substantial
8.5.2 Immunogenicity Assessments	The following text was added: Samples for determination of durvalumab concentration in serum will be analysed by a designated third party on behalf of AstraZeneca. Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual. Full details of the analytical method used will be described in a separate Bioanalytical Validation Report.	Revised per team input	Substantial
9.4.1. General considerations	The following text was added: "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. Participant 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."	Added in view of ongoing COVID-19 pandemic	Substantial
9.4.2 Efficacy	The following text was added for clarity under the sub-heading "Tumour response": "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 responder will be any participant with a confirmed response of PR or CR in their soft tissue disease assessed by RECIST 1.1, in the absence of progression on bone scan assessed by PCWG3. 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)."	Revised for clarity, per team input	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
9.4.2 Efficacy	The text for analysis of PROs was updated to omit the bone pain item, FAPSI-8 and box plot presentations, and to changed "time to worsening" to "time to **deterioration**" The following text was also omitted "~~Graphical presentations of safety data will be presented as is deemed appropriate. This may include, but is not restricted to, presentation of parameters against time, concentration or shift plots. Appropriate scatter plots will also be considered to investigate trends in parameters compared to baseline~~."	Revised per study team input	Substantial
9.4.4.1 Pharmacokinetic analysis	It was clarified that AZD4635's metabolites will be analyzed, and that durvalumab PK derivations are not planned. A note was added that "The PK parameter data may also be used to explore the relationship with other endpoints such as pharmacodynamics."	Updated per revisions made to the SAP	Substantial
Appendix B, B2. Definitions of serious adverse event	Clarification of reporting period for SAEs: "**If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate AstraZeneca representatives within one day i.e., immediately but no later than 24 hours of when they become aware of it.**"	Regulatory request to repeat in Appendix B the specific time-frame for reporting SAE.	Non-substantial
Appendix B, B2. Definitions of serious adverse event	Update to Appendix B2 to include text that was missing previously for tumour AEs: "**Adverse Events (AEs) for new malignant tumours reported during a study should generally be assessed as Serious AEs. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a Non-Serious AE. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfil the attributes for being**	Regulatory request to check text and include description of new malignancies.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
	assessed as serious, although reporting of the progression of the malignant tumour as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as Non-Serious; examples include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy."		
Appendix B, B5. Adverse Events of Special Interest	Section was added to include specific details of adverse events of special interest (AESI).	Regulatory request to update Appendix B with AESI details that were missing.	Substantial
Appendix H, PCWG3 Criteria	Text for Progression from nmCRPC to metastatic CRPC was omitted as it was not directly relevant to the study population.	Revised per team input	Non-substantial
Appendix I. Disallowed Medications	Clarifications have been made to describe the correct CYP3A inhibitors and inducers and remove redundant information/.	Updated to remove information which is not relevant to AZD4635 or cabazitaxel.	Substantial
Appendix L	Appendix L was added to the protocol, containing specifics regarding COVID, including a background to COVID-19, risk assessment in view of the COVID-19 pandemic, risk mitigation measures restrictions related to COVID-19 and data quality assurance considerations. References to the EMA and FDA guidances on the management and conduct of clinical trials during this pandemic were also provided.	Added in view of ongoing COVID-19 pandemic	Substantial
General	Minor updates throughout to correct typographical errors and for consistency in terminology.	Minor updates to correct typographical errors.	Non-substantial

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