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Clinical Study Protocol	
Drug Substance	AZD4635
Study Code	D8731C00001
Version	6.0
Date	June 24, 2021

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

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

VERSION HISTORY

Version 6.0, 24 June 2021

Global changes (strikethrough indicates deleted text):

- **Section 1.1 Synopsis** Study Chair amended to clarify that PPD is the new study chair.
- **Section 8.2.5 Electrocardiograms** amended to clarify that for all ECGs details of rhythm, PR, R-R, QRS and QT intervals and an overall evaluation will be recorded *on the eCRF*.

Version 5.0, 26 February 2021

Global changes (strikethrough indicates deleted text):

- **Section 2.3 Benefit/risk assessment** updated to reflect updated AZD4635 Investigator's brochure.
- **Section 2.3, Section 4.1.3, Section 7.1.2, Section 8.2.9, and Section 9.4.7** have been updated to include COVID-19 language.
- **Section 3 Study Objectives and Synopsis** has been revised to "*Patients with the presence or absence of anti-drug antibody (ADA)*"
- **Section 4.1 Overall Design, Figure 1, Figure 2** amended to clarify: The decision was made by the Sponsor not to open Module 3 to recruitment after a comprehensive strategy review of the AZD4635 program and not due to new dose-limiting toxicities or concerning safety signals observed with AZD4635.
- Updated core protocol to align with oleclumab Investigator's brochure.
- **Section 4.4 End of study definition** amended to clarify that *the end of study is defined as the last scheduled visit or contact of the last patient undergoing the study. There will be a primary analysis data cut-off (DCO) for the study (Modules 1 and 2 at approximately 6 months after the last patient starts investigational product (IP) or 90 days after the final patient discontinues IP if this is earlier). The clinical study database will be closed to new data after the DCO for the primary analysis.*
- **Section 5.2 Exclusion Criteria**:
  - Amended exclusion criterion 15 to clarify the sensitive substrates that would exclude patient participation.
- **Section 6.6.Concomitant medications, Table 6** and **Appendix J** updated to clarify prohibited sensitive substrates.
- **Section 6.6.1 COVID-19 Vaccination Guidance** has been added.
- **Section 6.8 Treatment after the end of the study** revised to reference primary DCO.
- **Section 8.2.8.3 Survival follow-up** has been amended to remain consistent with Section 9.4.4 and to clarify:

Version 5.0, 26 February 2021

  - Patients will be followed every 3 months after the last dose of study drug for survival until withdrawal of consent, or until the *primary* DCO for the study/module.

  ~~*Specifically these plots will be based on the sum of diameters as entered in the database, including no adjustment as a function of tumor response in the case of patients with lymph node regression.*~~

  - *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.*

- **Section 8.3.13 Safety data to be collected following the primary DCO of the study** has been added to the protocol.
- **Section 9 Statistical Considerations** amended to clarify that a comprehensive statistical analysis plan will be developed and finalized before database lock and will describe the patient populations to be included in the analyses *(performed by AstraZeneca and/or a third party)*, and procedures for accounting for missing, unused, and spurious data.
- **Section 9.2 and Synopsis** amended to clarify that *approximately* 20 patients will have RECIST measurable disease at baseline in each module.
- **Section 9.3 Population for analyses** has been revised and now includes "Dosed patients with at least 1 reportable PK concentration" Additionally, PK analysis guidelines have been revised.
- **Section 9.4.1 Definition of endpoints** has been revised to include durvalumab and oleclumab PK concentrations CCI [redacted] CCI [redacted]
- **Section 9.4.3 Exposure** has been updated to remove percent intended dose.
- **Section 9.4.6** has been revised CCI [redacted]

Version 4.0, 19 June 2020

Global changes:

- Addition of Module 3 - AZD4635 in combination with durvalumab and oleclumab (Appendix M)
- Updated core protocol to include Module 3 – AZD4635 in combination with durvalumab and oleclumab (Appendix M) which may proceed per Sponsor discretion and review of Module 2 data.
- **Section 1.1 Synopsis and Table 2, Section 4.1.2 Clinical screening procedures, and Section 8.1 Efficacy assessments** updated to clarify: *All patients are expected to have both CT/MRI/PET and bone scans at each scheduled disease assessment.*
- **Section 1.1 Synopsis and Section 3 Objectives and Endpoints** amended to clarify that multiple summaries from the Kaplan-Meier curve will be reported for radiological progression-free survival CCI [redacted]
- **Section 1.1 Synopsis and Section 9.2 Sample size determination** amended to clarify statistical methods for sample size determination.
- **Section 1.3 Schedule of Activities footnote f, Section 4.1.2 Clinical screening procedure, and Section 5.1 Inclusion Criteria #7** amended to clarify that a fresh biopsy will be required ~~at~~ *within 30 days of* screening, prior to the first dose of AZD4635, and at week 2 of AZD4635 study treatment, *prior to the administration of Cycle 1 Day 1 combinational agent*, for ~~a minimum of 15~~ *all* patients for each module *until there are sufficient paired samples for the analysis as determined by the Sponsor*.
- **Section 2.3 Benefit/risk assessment** updated to reflect updated AZD4635 Investigator's brochure.
- **Section 4.1.2 Clinical study procedures** amended to clarify that each potential patient will provide informed consent ≤ *28 days prior to the initiation of treatment and before* starting any study specific procedures.
- **Section 4.4 End of study definition** amended to clarify that *there will be a primary analysis data cut-off (DCO) for each module. A later DCO for the analysis of OS is also possible.*
- **Section 5.1 Inclusion Criteria**:
  - Added inclusion criterion 11 requiring patients to have a life expectancy of at least 12 weeks
- **Section 5.2 Exclusion Criteria**:
  - Added exclusion criterion 1 regarding eligibility of patients with secondary malignancies.
  - Added exclusion criterion 6 regarding eligibility of patients with prior history of myocardial infarction, transient ischemic attack, or stroke in the last 3 months.

Version 4.0, 19 June 2020

  - Amended exclusion criterion 7 to clarify that patients must have normotensive or well controlled BP (<*150*/90), with or without current antihypertensive treatment.
  - Amended exclusion criterion 12 to clarify that androgen-deprivation therapy is *required.*
  - Amended exclusion criterion 20 to clarify that patients should stop using these herbal medications 7 days prior to the first dose of AZD4635. *Exceptions may be agreed upon, but the circumstances must be reviewed by the Medical Monitor in advance.*
  - Amended exclusion criterion 24 to clarify eligibility of cardiac criteria to include *any concomitant medication with known or possible risk of QT interval prolongation. Patients receiving a medication(s) known to prolong QT interval may be discussed with the Medical Monitor or Sponsor for study approval.*
- **Section 7.3 Withdrawal from study** amended to clarify that data is to be collected at the time of study *drug* discontinuation and follow-up and for any further evaluations that need to be completed.
- **Section 8.1.1 Tumor assessments with RECIST v1.1** amended to clarify that if an unscheduled assessment is performed and the patient has not progressed, every attempt should be made to perform subsequent assessments at the scheduled visits ~~while the patient remains on study treatment~~.
- **Section 8.2.1 Clinical safety laboratory assessments and Table 8** amended to allow serum or plasma samples.
- **Section 8.2.1 Clinical safety laboratory assessments and Table 8** amended to add footnote "h" to clarify that *hepatitis A testing will only be performed if the patient is considered symptomatic per the Investigator*.
- **Section 8.2.5 Electrocardiograms** amended to add an end of treatment assessment.
- **Section 8.2.8.2 Progression-free follow-up visits and** amended to clarify that follow-ups will continue until withdrawal of consent*, or until the primary analysis DCO for the module,* or until the study or module is terminated by the Sponsor.
- **Section 8.2.8.3 Survival follow-up** amended to clarify that follow-ups will continue until *withdrawal of consent, or until the final DCO for the study/module*.
- **Section 8.4.5 Table 9** AZD4635 dose modifications for hematologic toxicities was removed. Based on current data this table is no longer appropriate.
- **Section 8.4.5.1 Hypertension** amended to allow systolic blood pressure of 150 mmHg.
- **Section 8.5.1 Determination of drug concentration** amended to clarify that any results from such analyses will be reported separately from the CSR, *but known metabolites will be reported in the CSR.*
- CCI [redacted]

Version 4.0, 19 June 2020

- CCI [redacted]
- CCI [redacted]
  CCI [redacted]
- **Section 9.4.4 Efficacy analysis** amended PSA response to clarify that Investigators should *ignore early rises (before 12 weeks) in determining PSA response*.
- **Section 9.4.4 Efficacy analysis** amended to clarify that tumor response data will be summarized for dosed patients with measurable disease at baseline and separately for dosed patients that ~~only~~ had *measurable and* non-measurable disease at baseline.
- **Section 9.4.4 Efficacy analysis** amended to clarify that overall survival is defined as the time from the *first dose of AZD4635* ~~date of randomization~~ until death due to any cause regardless of whether the patient withdraws from ~~randomized~~ *study* therapy or receives another anti-cancer therapy.
- **Section 9.4.5 Safety analyses** amended to clarify that safety data will not be formally analyzed but appropriate summaries for ~~all~~ safety data will be produced, as defined below. ~~At the end of the study, appropriate summaries for all safety data will be produced, as defined below.~~ All patients who received at least 1 dose of study drug will be included in the assessment of the safety profile (safety analysis set
- **Section 9.4.6 Other analyses** amended to clarify that *the analysis of the secondary endpoints PK, known metabolites and immunogenicity will be reported in the CSR* CCI [redacted]
- **Section 9.5 Interim analyses** amended to clarify that no *formal* interim analysis is planned. CCI [redacted]
- **Appendix A** was amended to add new regulatory reporting requirements for serious adverse events.
- **Appendix E** was amended to update Hy's Law and Potential Hy's Law guidance.

Version 3.0, 01 July 2019

Global changes:

Version 3.0, 01 July 2019

- CCI [redacted]
- **Section 4.4 End Study Definition** was amended to clarify that *the end of a module is defined as the last scheduled visit of the last patient undergoing the study within that specific module*.
- **Section 5.2 Exclusion criteria**:
  - Updated exclusion criterion 5 to clarify *if there is a diagnosis or history of hypertension, patient must have adequately controlled BP on ~~a maximum of~~ ~~2~~ antihypertensive medications, as demonstrated by 2 BP measurements taken in the clinical setting by a medical professional within 1 week prior to enrollment*.
  - Updated exclusion criterion 10 to clarify the interval between the end of the prior treatment and first dose of study drug for chemotherapy: ≥21 days or 5 half-lives (whichever is *shorter* ~~longer~~) of the first dose of study drug.
- **Section 8.1 Efficacy assessments** was updated to clarify: *All CT/bone scans and all imaging assessments performed for RECIST 1.1 tumour assessment will be reviewed at site. Duplicates must be available at the site in readiness to be sent for retrospective independent central RECIST 1.1 review, if deemed appropriate. More information on this procedure is available in the Image Acquisition Guideline for this study.*

Version 2.0, 22 May 2019

Changes to the protocol are summarised below in response to comments from the FDA received on the 20th May 2019.

- Section 5.2 Exclusion criteria:
  - Updating of exclusion criteria 2 from "*History of seizures, CNS tumors or metastasis"* to *"Previously untreated brain metastases. Patients who have received radiation or surgery for brain metastases are eligible if therapy was completed at least 21 days previously and there is no evidence of CNS disease progression or mild neurologic symptoms";*
  - Removal of exclusion criteria 6: *"Symptoms of a significant mental illness in the 4-week period preceding drug administration".*
- Section 4.3 Justification for dose: CCI [redacted]

Version 1.0, 10 April 2019
Initial creation

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.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Study Chair

PPD

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New York, NY 10032

Protocol Title:

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

Rationale:

AZD4635 appears to have increased efficacy in combination with anti-programmed death ligand 1 in prostate cancer due to increased immune activation compared to single agent AZD4635. On study D8730C00001 in the Phase 1A dose escalation portion, 12 patients with metastatic castrate-resistant prostate cancer were dosed with AZD4635, and prostate-specific antigen (PSA) responses were seen in 4 patients (2 in monotherapy and 2 in combination therapy). Three Response Evaluation Criteria in Solid Tumours responses were seen among these same patients with 1 complete response and 2 partial responses, all of which persisted for >6 months. Data from the ongoing Phase 1b portion of this study so far support the development of AZD4635 in combination in prostate cancer. Therefore, this open-label multi-center, modular Phase II study in patients with prostate cancer consists of a number of treatment cohorts, allowing evaluation of the efficacy, safety and tolerability of the study drug in multiple treatment arms.

Table 1 Study objectives	
Primary Objective:	**Endpoint/Variable:**
To evaluate efficacy of each combination therapy on objective response rate (ORR) for patients with measurable disease	Proportion of patients with measurable disease at baseline who have a confirmed ORR per Response Evaluation Criteria in Solid Tumours (RECIST 1.1)
To evaluate efficacy of each combination therapy on PSA response rate	PSA confirmed response is defined as the proportion of participants with a reduction in the PSA level of ≥50% from baseline to the lowest post-baseline PSA results, measured twice, at least 3 weeks apart by the Prostate Cancer Working Group 3 criteria (PCWG3)

Table 1 Study objectives	
Secondary Objectives:	**Endpoint/Variable:**
To evaluate the efficacy of each combination therapy on the proportion of patients alive and progression free at 6 months	Summaries of the Kaplan-Meier curve for radiological progression-free survival including the proportion of patients alive and radiological progression free at 6 months using RECIST 1.1 (soft tissue lesions) and PCWG3 (bone lesions)
To evaluate efficacy of each combination therapy on duration of response (DoR)	Duration of Response (DoR) is defined as the time from the date of first documented response until date of documented progression or death in the absence of disease progression
To evaluate efficacy of each combination therapy on overall survival (OS).	Overall survival is length of time from date of first dose until the date of death due to any cause.
To evaluate the pharmacokinetics (PK) of AZD4635 and its metabolites and other combination agent(s).	Steady state trough
To evaluate the immunogenicity of mAB study drug(s) in combination with AZD4635.	Patients with the presence or absence of anti-drug antibody (ADA)
Safety Objective:	**Endpoint/Variable:**
To assess the safety and tolerability of each treatment regimen.	Adverse events (AEs)/serious adverse events (SAEs) Physical exam and vital signs Collection of clinical chemistry/hematology parameters
Exploratory Objectives	**Endpoint/Variable:**
CCI	CCI
CCI	CCI
CCI	CCI
CCI	CCI
CCI	CCI

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

Overall design:

This is an open-label Phase II modular study in patients with prostate cancer which will assess safety, efficacy, and tolerability of AZD4635 in combination with other therapeutic agents in different treatment arms. The details of the study design, including identification of the combination agents, will be described in appendices to the core protocol. Three appendices are included in Study D8731C00001 as specified below. The decision was made by the Sponsor not to open Module 3 to recruitment after a comprehensive strategy review of the AZD4635 program and not due to new dose-limiting toxicities or concerning safety signals observed with AZD4635. Other combination agents may be identified and included in the study appendices under the auspices of appropriate IND or CTA amendments.

Appendix K Module 1: AZD4635 plus durvalumab

Appendix L Module 2: AZD4635 plus oleclumab

Appendix M Module 3: AZD4635 plus durvalumab plus oleclumab

All patients will be allocated into a module using the Interactive Web Response System (IWRS). Randomization will occur when patients meet eligibility criteria for 2 or more modules that are currently recruiting. If patients only meet the criteria for 1 currently recruiting module, they will be allocated to that module without randomization taking place.

Study Period:

Estimated date of first patient enrolled: Q3 2019

Estimated date of last patient completed: Q2 2021

Study site(s) and number of patients planned:

There will be approximately 30 patients with prostate cancer in each module. The intent is to conduct the study in multiple sites.

Treatments and treatment duration:

This protocol has a modular design, with the potential for future treatment arms to be added via protocol amendment. The core protocol has information about AZD4635 and refers to the following modules and study drugs. For specific information on each of the study drugs, please refer to the relevant module.

- Module 1: AZD4635 in combination with durvalumab
- Module 2: AZD4635 in combination with oleclumab
- Module 3: AZD4635 in combination with durvalumab and oleclumab

Additional modules and agents may be added as part of this multi-drug protocol as decisions on the most appropriate combinations to use become available. A substantial protocol amendment with relevant nonclinical and clinical data will be put in place before starting a new combination module.

Patients will continue to receive study treatment until one of the discontinuation criteria is met or withdrawal from study, whichever occurs first.

Statistical methods

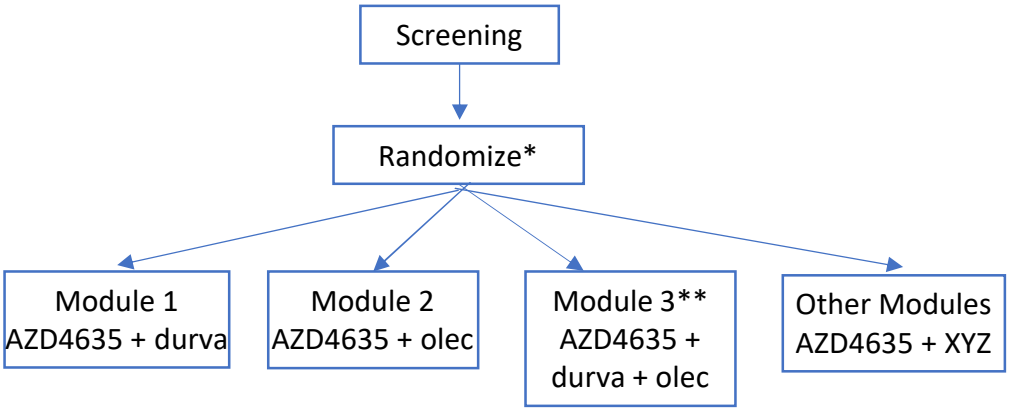
The primary efficacy endpoint is PSA decline from baseline ≥50% (PSA50) and overall response rate (ORR) per RECIST v1.1 for patients with measurable disease at baseline. In Modules 1, 2, and 3 (if conducted) there will be approximately 30 PSA evaluable patients in each module, and approximately 20 patients will have RECIST measurable disease at baseline in each module. Approximately 30 patients with and without measurable disease at baseline will be assessed for PSA50 in each module. For PSA50, 30% would be considered a good response rate. If the observed proportion of patients who have at least a PSA response of ≥50% from baseline is 30% and the sample size is 30, a two-sided 95% confidence interval for a single proportion using the exact Clopper-Pearson method will be (14.7%, 49.4%). Approximately 20 patients with measurable disease at baseline will be assessed for ORR in each module. For ORR, 25% would be considered a good response rate. If the observed proportion of patients who will have at least a best response of CR or PR is 25% and the sample size is 20, a two-sided 95% confidence interval for a single proportion using the exact

Clopper-Pearson method will be (8.7%, 49.1%). If any of the required patients for PSA and/or ORR are not evaluable for PSA response or tumor response, respectively, they may be replaced at the sponsor's discretion.

1.2 Schema

The general study design is summarized in Figure 1.

Figure 1 Study design



*if only eligible for one module, then patient will be allocated to that module rather than randomized
**The decision was made by the Sponsor not to open Module 3 to recruitment after a comprehensive strategy review of the AZD4635 program and not due to new dose-limiting toxicities or concerning safety signals observed with AZD4635.

The modular study design (Figure 2) may be found in Section 4.1.1.

1.3 Schedule of Activities (SoA) - Screening

The Schedule of Activities (SoA) for the pre-screening and screening visits is shown in Table 2 below. For the SoA to be performed during the on-treatment period, please refer to the relevant module.

Table 2 Schedule of Activities - Screening

Screening		Details in Section
Informed consent[a]	X	5.1
Inclusion/exclusion	X	5

Screening		Details in Section
Medical history and demographics[b]	X	4.1.2
Physical examination[b]	X	8.2.2
ECOG performance status[b]	X	8.2.3
Vital signs[b]	X	8.2.4
Height and weight[b]	X	8.2.4
12-lead ECG (triplicate) [b]	X	8.2.5
ECHO/ MUGA scan[b]	X	8.2.6
Hematology[b]	X	8.2.1
Clinical chemistry (including LDH, thyroid panel, and CRP) [b]	X	8.2.1
Testosterone sample[b]	X	8.2.1
Prostate-specific antigen (PSA)[d] CCI [redacted]	X	8.1.4
Urinalysis[b]	X	8.2.1
Coagulation test (PT/INR/aPTT)[b]	X	8.2.1
Hepatitis A, B, C; HIV-1[b]	X	8.2.1
Archival tumor sample[e]	X	8.8.2
Concomitant medication	X	6.6
Adverse event (AE) evaluation	X	8.3
Fresh tumor biopsy[f]	X	8.8.1.1
CCI [redacted]		
Tumor assessments CT/MRI/PET and Bone scans[c]	X	8.1.1

[a] Informed consent must be obtained ≤28 days prior to the initiation of treatment and before any study-specific procedures are performed.

[b] Assessments should be done ≤14 days prior to initiation of treatment. If these assessments are performed within 72 hours of initiation of treatment, they do not need to be repeated, with the exception of the ECOG performance status, abbreviated physical examination, vital signs (including respiration assessment) weight, and triplicate ECGs required prior to first study dose. The testosterone sample may be taken within 28 days of screening. Urinalysis should be repeated on Day 1 of every cycle, at the end-of-treatment (EOT) visit, and if clinically indicated. The Hepatitis A laboratory test should only be performed if the patient is considered symptomatic per the Investigator.

[c] Baseline tumor 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. Baseline tumor assessments should encompass all areas of known disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients as per investigator discretion. The methods of assessment used at baseline should be used at each subsequent follow-up assessment.

[d] Patients 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 pure small cell carcinoma). It is recommended to estimate a pretreatment PSA doubling time (PSADT) if at least 3 values are available ≥4 weeks apart. Treatment or enrollment onto a trial should not be delayed to estimate PSADT.

[e] All patients will be required to provide a sample of their archival tumor, if available (tissue from the primary lesion or a metastatic site is acceptable). The archived tumor samples will preferably be in the form of a formalin fixed paraffin embedded (FFPE) block. If archival tumor tissue is not available, then tissue from a fresh tumor biopsy is required.

[f] All patients will be required to have a site of disease that is safely accessible for biopsy (paired) upon enrolment unless there are sufficient paired samples for the analysis as determined by the Sponsor . The initial predose biopsy should be taken within 30 days of screening (at least 1 day prior to the first administration of AZD4635) and 2 weeks after the initiation of AZD4635 therapy. A 5-day window is permitted to facilitate on-treatment biopsy collection (Days 12 - 16 post first dose of AZD4635). The time and site of the biopsy must be clearly documented. Instructions for processing of biopsies are in the laboratory manual.

CCI [redacted]

2 INTRODUCTION

Prostate cancer is the second most frequently diagnosed cancer in men and was estimated to be responsible for over 300,000 deaths worldwide in 2018 (Bray et al. 2018). For patients who require systemic therapy, the mainstay of treatment is hormonal therapy but patients often develop resistance to this therapy (castrate resistant prostate cancer). Treatment for both metastatic and non-metastatic prostate cancer is rapidly evolving. Since the development of a docetaxel regimen for the treatment of metastatic castration-resistant prostate cancer (mCRPC) in 2004 (Tannock et al. 2014), the outcomes of this condition have improved dramatically. However, many of the treatments for prostate cancer, including docetaxel and cabazitaxel for mCRPC, may not be suitable for all patients and some patients are refractory to these treatments, thus there remains a need for additional therapies for this disease.

Current standard of care (SOC) therapies for mCRPC include enzalutamide, and abiraterone plus prednisone. Enzalutamide, a targeted androgen-receptor inhibitor that blocks 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 and metastatic castration-sensitive prostate cancer (mCSPC). 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) and for metastatic high-risk castration-sensitive prostate cancer.

2.1 Study rationale

Although there are now standard of care (SOC) treatments for mCRPC, better treatments are needed for patients after the SOC options have been exhausted.

AZD4635 is being developed as monotherapy and in combination with other agents to augment the anti-tumor immune response. Ongoing studies D8730C00001 and D6070C00004 include the combination of AZD4635 with durvalumab (anti-PDL1 monoclonal antibody) as well as in combination with oleclumab (CD73 mAb), respectively. On study D8730C00001 in the Phase 1A dose escalation portion, 12 patients with metastatic CRPC were dosed with AZD4635, and PSA responses were seen in 4 patients (2 in monotherapy and 2 in combination therapy). Three RECIST responses were seen among these same patients with 1 CR and 2 PRs, all of which persisted for >6 months. Data for the ongoing Phase 1b portion of the study so far support the development of AZD4635 in combination in prostate cancer. Therefore, this open-label multi-center, modular Phase II study in patients with prostate cancer consists of a number of treatment cohorts, allowing evaluation of the efficacy, safety and tolerability of the study drug in multiple treatment arms.

Study rationale for each module is provided in the modular-specific appendix.

2.2 Background

T-cell-mediated immune responses to treatment with immune checkpoint inhibitors have been shown to induce durable responses in several cancers (Larkin et al. 2015, Robert et al. 2015, Brahmer et al. 2015, McDermott et al. 2015, Le et al. 2015, Antonia et al. 2017). However, immune suppression in the tumor microenvironment (TME) can lead to immune evasion, decrease effectiveness of T cells, and impact primary resistance or acquired resistance to immunotherapy. Extracellular adenosine signaling through adenosine 2a receptor ($A_{2A}R$) is one such mediator of immune suppression which leads to decreases in antigen presentation and T cell activation, as well as an increase in suppressive cells. Modulation of the TME with drugs that decrease adenosine or inhibit the $A_{2A}R$ may reverse these effects and enable the host to mount an effective anti-tumor immune response, even in tumor types that are not typically responsive to immune checkpoint inhibitors.

AZD4635 is a potent, highly selective inhibitor of $A_{2A}R$. In preclinical mechanistic, efficacy and pharmacodynamic (PDx) studies, AZD4635 demonstrates activity consistent with enhancement of antitumor immunity. CCI

[redacted]

AZD4635 appears to have increased efficacy in combination with anti-programmed death ligand 1 in prostate cancer due to increased immune activation compared to single agent AZD4635. As of October 4, 2018, in the ongoing study D8730C00001, prostate-specific antigen (PSA) responses were seen in 4 of 10 patients with advanced prostate cancer (2 patients in AZD4635 monotherapy [Phase 1a], and 2 patients receiving AZD4635 in combination with durvalumab [Phase 1a]). In Phase 1a, 8 patients had disease measurable by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) and were observed to have 2 partial responses (1 in a monotherapy cohort, 1 in AZD4635 + durvalumab combination cohorts) and 1 complete response (in an AZD4635 + durvalumab combination cohort). All of these responses persisted for >6 months (11-16 months). Data from this ongoing study appear to suggest a higher response rate in prostate cancer following combination therapy with AZD4635 + durvalumab over AZD4635 monotherapy. Although the combination of anti-CD73 (oleclumab) with AZD4635 has not been studied specifically in

prostate cancer, there is an ongoing study of oleclumab with AZD4635 in refractory epidermal growth factor receptor (EGFR)-mutant non-small cell lung cancer (NSCLC) post-tyrosine kinase inhibitor (TKI) progression. This combination provides inhibition of the adenosine axis by both reduction of adenosine production plus $A_{2A}R$ blockade and is hypothesized to increase the response seen with either single agent alone by further diminishing the adenosine mediated immunosuppression. This hypothesis is also applicable to patients with prostate cancer.

A detailed description of the chemistry, pharmacology, efficacy, and safety of AZD4635 is provided in the Investigator's Brochure (IB).

2.3 Benefit/risk assessment

AZD4635 is a novel $A_{2A}R$ antagonist agent that acts against cancer by blocking adenosine-mediated $A_{2A}R$ signaling in tumor infiltrating cells. AZD4635 blockade is hypothesized to modulate the TME so that an active anti-tumor immune response will be more effective. Therefore, AZD4635 may have the potential to provide benefit in terms of increased efficacy in patients with a variety of advanced solid malignancies and for patients who are refractory to SOC treatments.

As of December 2019, approximately 300 patients with advanced cancer had been treated with AZD4635 alone or in combination with another cancer drug. Between 30 August 2016 and 20 June 2019 (date of data cut-off) in the ongoing study D8730C00001, 94 mCRPC patients were treated with AZD4635 (125 mg BID, 75 mg QD, or 100 mg QD oral nanosuspension Q3W monotherapy [n=49]) or in combination (75 or 100 mg QD) with durvalumab 1.5g IV Q4W (n=45).

As of December 17, 2018, 17 healthy volunteers had received AZD4635 nanosuspension or AZD4635 capsule formulation in study D8730C00002. As of October 05, 2018 in study D6070C00004, 8 patients had received AZD4635 at 2 dose levels in combination with oleclumab.

Based on the available safety data, there are currently no identified risks for AZD4635 when it is used as monotherapy or given in combination with durvalumab or oleclumab. In study D8730C00001, 2 serious adverse events (SAEs) were reported for AZD4635 (at various dose levels) in combination with durvalumab which were considered related to study treatment by the investigators: diabetes mellitus type 1 (Grade 4) and hypertension (Grade 3). In Study D6070C00004, 1 SAE of pulmonary embolism (Grade 3) was considered related to the combination of AZD4635 and oleclumab by the Investigator. Although, thrombosis is considered to be an important potential risk for oleclumab based on known mechanism of action, it is not considered to be a risk for AZD4635.

The most common treatment-emergent AEs (TEAEs) seen in patients treated with AZD4635 as monotherapy or in combination across all studies were mainly nausea, vomiting and fatigue. These AEs were mostly Grade 1 or 2 and were clinically manageable. One patient in study D8730C00001, in the Phase 1a dose-escalation cohort of the combination (75 mg AZD4635 + 1500 mg durvalumab), experienced Grade 2 dose-limiting toxicities (DLTs) of nausea and fatigue which required dose reduction of AZD4635 to 50 mg.

In study D8730C00001, 70 patients were evaluable for tumor 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% confidence interval [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 patients; 95% CI, 1.3-17.5%) and combination=20% (9/45 participants; 95% CI, 9.6 34.6%).

More detailed information about the known and expected benefits and risks and reasonably expected AEs of each study drug may be found in their drug-specific IBs and the relevant modules. Appendix A in Modules 1 and 2 describes risk considerations for COVID-19.

3 OBJECTIVES AND ENDPOINTS

Table 3 Study objectives	
Primary Objective:	**Endpoint/Variable:**
To evaluate efficacy of each combination therapy on objective response rate (ORR) for patients with measurable disease	Proportion of patients with measurable disease at baseline who have a confirmed ORR per Response Evaluation Criteria in Solid Tumours (RECIST 1.1)
To evaluate efficacy of each combination therapy on PSA response rate	PSA confirmed response is defined as the proportion of participants with a reduction in the PSA level of ≥50% from baseline to the lowest post-baseline PSA results, measured twice, at least 3 weeks apart by the Prostate Cancer Working Group 3 criteria (PCWG3)
Secondary Objectives:	**Endpoint/Variable:**
To evaluate the efficacy of each combination therapy on the proportion of patients alive and progression free at 6 months	Summaries of the Kaplan-Meier curve for radiological progression-free survival including the proportion of patients alive and radiological progression free at 6 months using RECIST 1.1 (soft tissue lesions) and PCWG3 (bone lesions)
To evaluate efficacy of each combination therapy on duration of response (DoR)	Duration of Response (DoR) is defined as the time from the date of first documented response until date of documented progression or death in the absence of disease progression
To evaluate efficacy of each combination therapy on overall survival (OS).	Overall survival is length of time from date of first dose until the date of death due to any cause.

Table 3 Study objectives	
To evaluate the pharmacokinetics (PK) of AZD4635 and its metabolites and other combination agent(s).	Steady state trough
To evaluate the immunogenicity of mAB study drug(s) in combination with AZD4635.	Patients with the presence or absence of anti-drug antibody (ADA)
Safety Objective:	**Endpoint/Variable:**
To assess the safety and tolerability of each treatment regimen.	AEs/SAEs Physical exam and vital signs Collection of clinical chemistry/hematology parameters
Exploratory Objectives	**Endpoint/Variable:**
CCI	CCI
CCI	CCI
CCI	CCI
CCI	CCI
CCI	CCI
CCI	CCI
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CCI	CCI
CCI	CCI

Table 3 Study objectives	
CCI	CCI

4 STUDY DESIGN

4.1 Overall design

This is an open-label Phase II modular study in patients with prostate cancer to assess safety, efficacy, and tolerability of AZD4635 in combination with other therapeutic agents in different treatment modules. Patients will be randomized for inclusion in the initial 3 modules of AZD4635 plus durvalumab, AZD4635 plus oleclumab, and AZD4635 plus durvalumab plus oleclumab. The decision was made by the Sponsor not to open Module 3 to recruitment after a comprehensive strategy review of the AZD4635 program and not due to new dose-limiting toxicities or concerning safety signals observed with AZD4635.. Patients will be dosed with the capsule formulation of AZD4635.

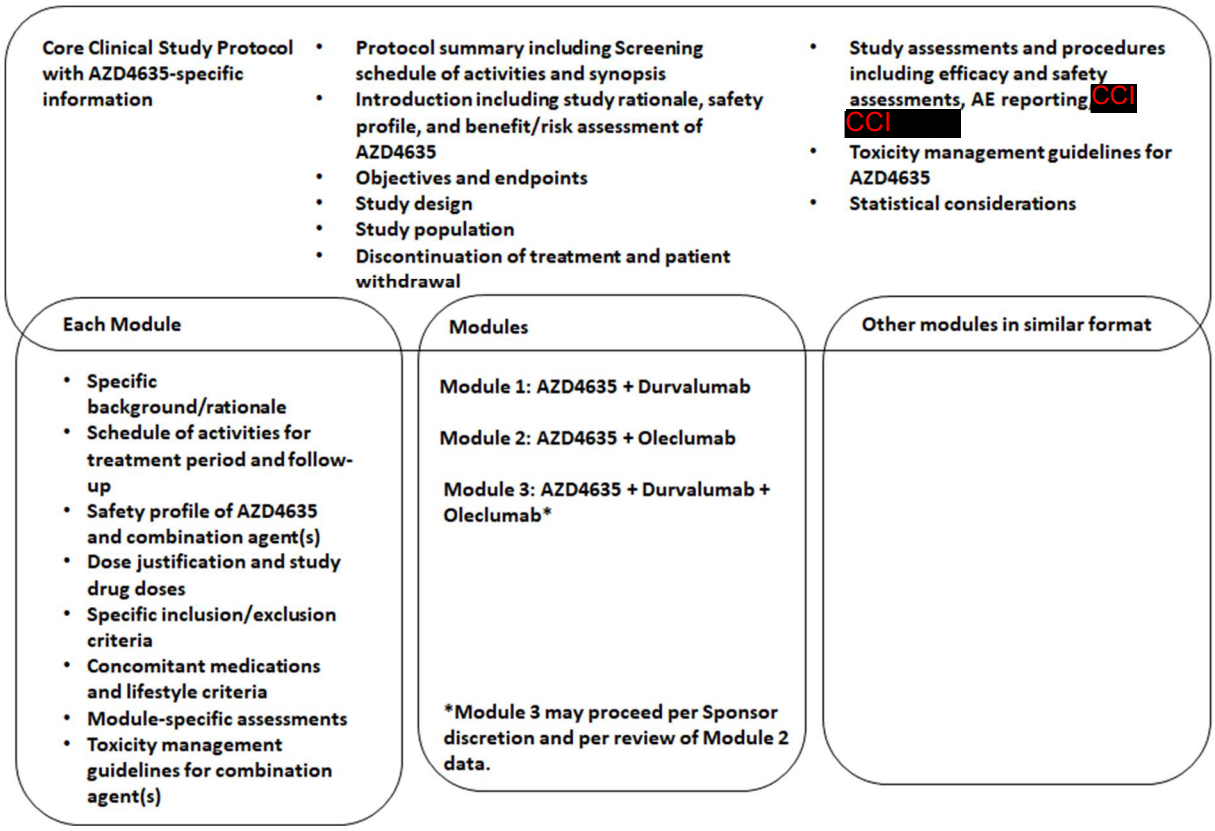
For an overview of the study design see Figure 1, Section 1.2. For details on treatments given during the study, see Section 6.1 Treatments Administered.

For details on what is included in the efficacy and safety endpoints, see Section 3 Objectives and Endpoints.

4.1.1 Modular protocol structure

This study is modular in design and has the potential to include new study drugs in the future via addition of further modules. Information relating to the overall study, including study objectives, rationale, core inclusion and exclusion criteria, safety assessments, and AE reporting can be found in the core protocol. Toxicity management guidelines for AZD4635 are found in Section 8.4.5.

Figure 2 Modular study design[a]



[a] The decision was made by the Sponsor not to open Module 3 to recruitment after a comprehensive strategy review of the AZD4635 program and not due to new dose-limiting toxicities or concerning safety signals observed with AZD4635.

Study drug-specific information including doses and justifications, toxicity management, dose modifications and concomitant medications for AZD4635 can be found in the core protocol. Study drug-specific information including doses and justifications, toxicity management, dose modifications and concomitant medications for additional study agents can be found in the relevant module.

4.1.1.1 List of modules

The following modules for the study are included with this protocol. The structure of the protocol allows for further modules to be added to the core study via protocol amendment as required.

- Module 1: AZD4635 in combination with durvalumab (Appendix K)
- Module 2: AZD4635 in combination with oleclumab (Appendix L)
- Module 3: AZD4635 in combination with durvalumab and oleclumab (Appendix M)

As stated above, the modules contain study drug-specific information. Specific rationales for these cohorts are provided in the modules.

4.1.2 Clinical screening procedures

Each potential patient will provide informed consent ≤ 28 days prior to the initiation of treatment and before starting any study specific procedures.

Following patient consent, data obtained prior to consent may be used for screening provided the assessments fall within the protocol-specified period prior to the first dose of study drug.

The following screening procedures, which are common to each of the modules, should be performed (please also refer to Table 2):

- Demographic data and other characteristics will be recorded and will include date of birth or age, gender, and race and/or ethnicity per local regulations.
- A standard medical, medication and surgical history, including prior cancer treatments, response, and duration of prior therapy, will be obtained.
- The following clinical assessments will be required:
    - Physical examination and ECOG performance status evaluation
    - Vital signs + weight and height
    - ECG
    - ECHO/MUGA scan
    - Blood samples collection including testosterone and PSA
    - Urine sample collection
    - Tumor assessments: CT/MRI/PET and Bone scans per RECIST v.1.1 and PCWG3
- All patients will be required to provide an archival tumor block (if available) or a new fresh tumor biopsy if an archival sample is not available (this biopsy sample is not to replace the fresh paired biopsy collection described below).
- A fresh biopsy will be required within 30 days of screening, prior to the first dose of AZD4635, and at week 2 of AZD4635 study treatment, prior to the administration of Cycle 1 Day 1 combinational agent, for all patients for each module until there are sufficient paired samples for the analysis as determined by the Sponsor. In the case that the second sample is not taken, the patient will remain in the study, and there will be no penalty or loss of benefit to the patient, and they will not be excluded from other aspects of the study. The requirement for biopsies must be made clear to each patient at the time of initial approach by the Investigator.
- At screening, consenting patients are assessed to ensure that they meet the core and module-specific eligibility criteria for one or more modules.
- All eligible patients will then be assigned into a module via IWRS system. Randomization will occur when patients meet eligibility criteria for 2 or more modules that are currently recruiting**. If patients only meet the criteria for 1 currently recruiting module, they will be allocated to that module without randomization taking place.**

- All patients, after being assigned into a module, will need to consent for a module specific ICF prior to the 1st dose on study.

Samples for laboratory tests for the assessment of safety will be sent to a local laboratory and assessed locally. All other samples such as those for the assessment of molecular aberrations CCI will be assessed centrally. The tumor sample(s) taken as part of the screening procedures will be sent to a central laboratory(ies) for analysis of molecular alterations using tests verified and validated in line with local regulations e.g., Clinical Laboratory Improvement Amendments/College of American Pathologists (CLIA/CAP) for US laboratories, Good Clinical Practice (GCP), and local accreditation for other territories.

4.1.3 COVID-19 testing (if applicable)

During the study, tests for active coronavirus disease of 2019 (COVID-19) infection may be conducted, if required, and in accordance with local guidance.

If a patient is symptomatic for active COVID-19 infection during a site visit, they 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/Study Physician should be consulted. If a patient tests 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/Study Physician. Where applicable, home, or remote visits may be conducted for study assessments and study drug administration (refer to Appendix A in Modules 1 and 2).

4.2 Scientific rationale for study design

Although there are now SOC treatments for prostate cancer, better treatments are needed for patients after the SOC options have been exhausted. AZD4635 is being developed as monotherapy and as an immuno-oncology agent in combination with durvalumab (MEDI4736, PD-L1 monoclonal antibody [mAb]) and in combination with oleclumab (MEDI9447, CD73 mAb), exploiting complementary immune-related mechanisms to broaden and deepen clinical responses in prostate cancer.

AZD4635 had been studied clinically in 3 other investigational trials prior to initiation of this protocol:

- D8730C00001 (NCT02740985): This first-time-in-human (FTIH) study of AZD4635 is a Phase 1 study that dosed AZD4635 at the maximum tolerated dose (MTD) of 100 mg orally (PO) daily (QD) both as monotherapy and in combination with durvalumab in patients with advanced solid tumors.
- D8730C00002 (NCT02740985): A bioavailability study in healthy volunteers was undertaken in order to facilitate a change in formulation and compare the performance of a capsule formulation to the existing nano-suspension to assess the 2 formulation variants.

- D6070C00004 (NCT03381274): AZD4635 is also being studied at 75 and 50 mg PO QD in combination with oleclumab (MEDI9447) 1500 mg intravenously (IV) every 2 weeks (Q2W) in patients with refractory EGFRm lung cancer. Patients developed significant nausea and vomiting at the starting dose of AZD4635 75 mg QD + oleclumab 1500 mg. However, dose reduction to 50 mg AZD4635 nanosuspension daily in combination with oleclumab 1500 mg IV is still under evaluation.

Please see the AZD4635 IB for more information.

4.3 Justification for AZD4635 dose

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[redacted]

CCI

[redacted]

Information on dose justification for other study drugs is provided in the respective modules.

4.4 End of study definition

The end of study is defined as the last scheduled visit or contact of the last patient undergoing the study. There will be a primary analysis data cut-off (DCO) for the study (Modules 1 and 2) at approximately 6 months after the last patient starts investigational product (IP) or 90 days after the final patient discontinues IP if this is earlier. The clinical study database will be closed to new data after the DCO for the primary analysis.

The study may be terminated at individual centers if the study procedures are not being performed according to Good Clinical Practice (GCP) or if the site is unable to recruit sufficient numbers of patients into the study.

The AstraZeneca Study Team may also terminate the entire study or individual modules prematurely if concerns for safety arise within this study or in any other study with any agent used in any of the study treatments.

Any patients still receiving IP at the time of the primary study data cut-off can either choose to discontinue from the study or keep receiving IP while deriving clinical benefit as per investigator discretion, following discussion with and approval from the AstraZeneca Study Team. See section 6.8 of this protocol for more information on treatment after the end of this study.

See Appendix A 6 for a description of where protocol information and study results will be made publicly available.

5 STUDY POPULATION

Prospective approval of a protocol deviation from recruitment and enrollment criteria, also known as a protocol waiver or exemption, is not permitted.

Each patient must meet all of the inclusion criteria and none of the exclusion criteria for this study in order to be assigned/randomized to a study module. Under no circumstances can there be exceptions to this rule. Patients who do not meet the entry requirements are screen failures (refer to Section 5.4).

Where there are differences in stringency or cut-off values between the core protocol and specific module, the specific module takes precedence. For example, if hematological or medication parameters are stricter in the module than in the core protocol, the Investigator should adhere to the module criteria.

In this protocol, "enrolled" patients are defined as those who sign informed consent forms (ICFs). "Randomized" patients are defined as those who undergo randomization and receive a randomization number or are assigned to a module.

For procedures for withdrawal of incorrectly enrolled patients see Section 7.3.

5.1 Inclusion criteria

The inclusion criteria that are applicable to all patients in the study are described in this section. Please also refer to the relevant module protocol for specific criteria applicable to each module.

Inclusion Criteria for all patients in all modules

Patients are eligible to be included in the study only if all of the following inclusion criteria are met and none of the exclusion criteria apply:

Informed consent

1 Ability to provide signed informed consent, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

2 Provision of signed and dated, written informed consent form prior to any mandatory study specific procedures, sampling, and analyses.

CCI [redacted]

The ICF process is described in Appendix A 3. CCI [redacted]

Age

3 Patient must be ≥18 years of age at the time of signing the ICF.

Type of patient and disease characteristics

4 Patients must have prostate cancer with histological or cytological confirmation.

5 Patients must have previously received and progressed on standard-of-care therapy(ies).

6 Patients must be able to provide an archival tumor tissue. If archival tumor tissue is not available, then tissue from a fresh tumor biopsy is required.

7 All patients will be required to have a site of disease that is safely accessible for biopsy (paired) upon enrollment unless there are sufficient paired samples for the analysis as determined by the Sponsor. Accessible lesions are defined as those which are biopsiable (at screening) and amenable to repeat biopsy (after 2 weeks of AZD4635 therapy), unless clinically contraindicated.

The provision of paired biopsies will be closely monitored to ensure the desired number of biopsiable patients are enrolled and investigators are aware of this requirement at all times.

8 Patients with measurable diseases must have:

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

Or

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

9 Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 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.

10 Ability to swallow and retain oral medication.

11 Must have a life expectancy of at least 12 weeks

Sex

12 Male

Weight

13 Body weight ≥35 kg at screening

Reproduction

14 Willingness to adhere to the study treatment-specific contraception requirements: Male patients must be surgically sterile or using an acceptable method of contraception

(defined as barrier methods in conjunction with spermicides) for the duration of the study (from the time they sign ICF) and for 3 months after the last dose of AZD4635 to prevent pregnancy in a female partner. Male patients must not donate or bank sperm for 24 weeks after treatment.

A more detailed description of the required lifestyle restrictions relating to reproduction is provided in Section 5.3.2.

5.2 Exclusion criteria

The exclusion criteria that are applicable to all patients in the study are described in this section. Please also refer to each specific module protocol for specific criteria applicable to each module.

Exclusion Criteria for all patients in all modules

Patients must not enter the study if any of the following exclusion criteria apply:

Medical conditions

1 History or presence of another primary invasive malignancy except for:
   - Malignancy treated with curative intent and with no known active disease ≥2 years before the first dose of study drug and of low potential risk for recurrence.
   - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.
   - Adequately treated carcinoma *in situ* without evidence of disease.
   - Localized non-invasive primary carcinoma under surveillance.

2 Refractory nausea and vomiting, chronic gastrointestinal diseases, or previous significant small bowel resection that would preclude adequate absorption of AZD4635.

3 Previously untreated brain metastases. Patients who have received radiation or surgery for brain metastases are eligible if therapy was completed at least 21 days previously and there is no evidence of CNS disease progression or mild neurologic symptoms

4 With the exception of alopecia, lymphopenia, and hypothyroidism, any unresolved toxicities from prior therapy greater than National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v5.0) Grade 1 at the time of starting study treatment.

5 Patients with prior ≥ Grade 3, serious, or life threatening immune-mediated reactions following prior anti-PD-1, anti-PD-L1, or other immuno-oncology therapies.

6 Prior history of myocardial infarction, transient ischemic attack, or stroke in the last 3 months.

7 Patients must have normotensive or well controlled BP (<150/90), with or without current antihypertensive treatment. If there is a diagnosis or history of hypertension, patient must have adequately controlled BP on antihypertensive medications, as demonstrated by 2 BP measurements taken in the clinical setting by a medical professional within 1 week prior to enrollment. Patients on a hypertensive medication must be willing and able to measure and record BP readings twice-daily for a minimum of 3 weeks.

8 As judged by the Investigator or Medical Monitor, any evidence of severe or uncontrolled systemic diseases, including active bleeding diatheses, or active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and tuberculosis testing in line with local practice), hepatitis B virus (known positive HBV surface antigen (HBsAg) result), hepatitis C, or human immunodeficiency virus (positive HIV 1/2 antibodies). Active hepatitis A as judged by the Investigator. Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA. Screening for chronic conditions is not required.

9 Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., colitis, Crohn's disease], diverticulitis, celiac disease, systemic lupus erythematous, Wegener's syndrome, myasthenia gravis, Grave's disease, rheumatoid arthritis, hypophysitis, uveitis, autoimmune pneumonitis, autoimmune nephritis or nephropathy, etc.) within the past 3 years prior to the start of treatment. The following are exceptions to this criterion:

- Vitiligo or alopecia
- Hypothyroidism (e.g., following Hashimoto's disease) stable on hormone replacement
- Psoriasis or eczema not requiring systemic therapy for disease control
- Celiac disease controlled by diet alone.

Prior/concomitant therapy

10 Prior therapy with AZD4635 or any other $A_{2A}R$ antagonist.

11 Ongoing corticosteroid use, at doses above physiologic replacement therapy. The following are exceptions to this criterion:

- Use of intranasal, inhaled, topical corticosteroids, local steroid injections (e.g. intra-articular injections)
- Steroids as premedication for hypersensitivity reactions (e.g. CT scan premedication) are permitted

- Systemic corticosteroids at physiologic doses below 10 mg/day of prednisone or equivalent.

12 The following intervals between the end of the prior treatment and first dose of study drug must be observed:

- Anticancer therapy: ≥21 days or 5 half-lives (whichever is shorter) of the first dose of study drug. At least 7 days must have elapsed between the last dose of such agent and the first dose of study drug. **Exception:** Androgen-deprivation therapy is required to maintain castrate levels of testosterone (<50 ng/dL).
- Concurrent use of hormones for non-cancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable.

13 Major surgery (as defined by the Medical Monitor, excluding placement of vascular access) within 4 weeks of the first dose of study treatment.

14 Minor surgical procedures (as defined by the Medical Monitor) within 7 days of the first dose of study treatment

15 Patient is receiving medications or other products known to be sensitive breast cancer resistance protein (BCRP) or organic anion transporter polypeptide 1 (OATP1B1), OATP1B3, OAT1, organic cation transporter 1 (OCT1), OCT2, multidrug and toxin extrusion protein 1 (MATE1) and P-glycoprotein (P-gp) substrates or potent or moderate inhibitors/inducers of CYP1A2, 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 AZD4635. See Appendix J for the list of BCRP, OATP1B1, OATP1B3, OAT1, OCT1, OCT2, MATE1 and P-gp substrates, and CYP1A2 inhibitors and inducers.

16 Concomitant medications with another A_1R antagonist that would increase risk of seizure (e.g., theophylline, aminophylline).

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

18 Ongoing treatment with Coumadin.

19 Receipt of live attenuated vaccine within 30 days prior to the first dose of study drug.

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), ginkgo biloba, dehydroepiandrosterone, yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 7 days prior to the first dose of AZD4635. Exceptions may be agreed upon, but the circumstances must be reviewed by the Medical Monitor in advance.

21 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 treatment.

22 Enrollment into another therapeutic clinical trial. **Exception:** Patients are allowed to participate in investigational imaging or non-interventional studies.

23 History of hypersensitivity to AZD4635 or drugs with a similar chemical structure or class to AZD4635.

Diagnostic assessments

24 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 concomitant medication with known risk of QT interval prolongation. Patients receiving a medication(s) known to prolong the QT interval may be discussed with the Medical Monitor or Sponsor for study approval.
- Ejection fraction <55% or the lower limit of normal of the institutional standard.

25 Inadequate bone marrow reserve or organ function as demonstrated by any of the following laboratory values:

- Absolute neutrophil count <1.5 x 10^9/L
- Platelet count <100 x 10^9/L
- Hemoglobin <9.0 g/dL
- Alanine aminotransferase (ALT) >2.5 times the upper limit of normal (ULN) if no demonstrable liver metastases or >5 times ULN in the presence of liver metastases
- Aspartate aminotransferase (AST) >2.5 times ULN if no demonstrable liver metastases or >5 times ULN in the presence of liver metastases
- Total bilirubin (TBL) >1.5 times ULN
- Creatinine >1.5 times ULN concurrent with creatinine clearance <50 mL/min (measured or calculated by Cockcroft and Gault equation); confirmation of creatinine clearance is only required when creatinine is >1.5 times ULN.

Other exclusions

26 Involvement in the planning and/or conduct of the study (applies to AstraZeneca staff and its representatives and/or staff at the study site).

27 Judgment by the Investigator or Medical Monitor that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions and requirements.

28 Participation in another clinical interventional study or if patient has already received at least one dose of study drug in the present study.

CCI [redacted]

CCI [redacted]

5.3 Lifestyle restrictions

Please refer to the relevant modules. Where restrictions are more stringent in the module rather than the core protocol, the Investigator should adhere to the module criteria.

5.3.1 Meals and dietary restrictions

Whenever possible, all doses of AZD4635 should be taken at approximately the same times each day with or without food.

5.3.2 Reproduction

The following restrictions apply while the patient is receiving AZD4635 study treatment and for the specified times before and after:

- Male patients should be asked to avoid unprotected sex with women of child-bearing potential during the study and for a washout period of 3 months after discontinuing study treatment. Patients should refrain from donating sperm from the start of dosing until 24 weeks after discontinuing study treatment. If male patients wish to father children they should be advised to arrange for freezing of sperm samples prior to the start of study treatment.
- Female partners (of childbearing potential) of male patients must also use a highly effective method of contraception throughout this period.

Highly effective methods of contraception, defined as those that result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly, are described in Table 4. Note that some contraception methods are not considered highly effective (e.g., male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non-copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding Cerazette/desogestrel which is considered highly effective]; and triphasic combined oral contraceptive pills).

Table 4 Highly effective methods of contraception (<1% failure rate)

Barrier/intrauterine methods	Hormonal methods
• Copper T intrauterine device • Levonorgestrel-releasing intrauterine system (e.g., Mirena®)[a]	• Implants: Etonogestrel-releasing implants (eg, Implanon® or Norplant®) • Intravaginal Devices: Ethinylestradiol/etonogestrel-releasing intravaginal devices (eg, NuvaRing®) • Injection: Medroxyprogesterone injection (eg, Depo-Provera®) • Combined Pill: Normal and low dose combined oral contraceptive pill • Patch: Norelgestromin/ethinylestradiol-releasing transdermal system (eg, Ortho Evra®) • Minipill: Progesterone based oral contraceptive pill using desogestrel: Cerazette® is currently the only highly effective progesterone based pill

[a] This is also considered a hormonal method

Please follow module-specific guidance for reproduction information on other study treatment.

5.4 Screen failures

Screen failures are defined as patients who sign the ICF to participate in the clinical study but are not subsequently randomly assigned to study treatment or do not meet the criteria for participation in the study.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients 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.

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

- Patients 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.
- Patients for whom Screening procedures are not completed within the 28-day window.

- Patients 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.

Patients may not be rescreened if they had previously concluded screening and had already been allocated to a module. However, 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.

6 STUDY TREATMENTS

Please refer to each modular-specific appendix for details of the investigational products (IPs) that are applicable to each module of the study. Details for AZD4635 capsule (which will be used in each module) are described in this section.

6.1 Treatments administered

6.1.1 Investigational products

AZD4635	
Study treatment name:	AZD4635
Dosage formulation:	Capsule
Route of administration	Oral
Dosing instructions:	Whenever possible, all doses of AZD4635 should be taken at approximately the same times each day with or without food. Should a patient miss a scheduled dose, the patient 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, the missed dose should not be taken, and the patient should take the allotted dose at the next scheduled time. If a patient needs to take the dose earlier for any reason, the patient can take the dose up to 4 hours earlier than the scheduled dose time. The patient should make every reasonable effort to take the study drugs on time.
Packaging and labeling	Study treatment will be provided in high-density polyethylene (HDPE) bottles induction-sealed with desiccant. Each bottle will be labeled in accordance with Good Manufacturing Practice (GMP) Annex 13 and per country regulatory requirements.

6.2 Preparation/handling/storage/accountability

AZD4635 capsule should be stored in the pack provided according to the storage conditions on the label.

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

Only patients enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

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

Further guidance and information for the final disposition of unused study treatment are provided in the module-specific pharmacy manual.

6.3 Measures to minimize bias

This is an open-label study. Recruitment to each module will be centrally assigned using IWRS. Before the study is initiated, the log-in information and directions for the IWRS will be provided to each site. Potential bias will be reduced by central randomization, whenever 2 or more modules are currently recruiting as follows:

All patients will be assigned into a module via IWRS system. Randomization will only occur when patients meet eligibility criteria for 2 or more modules that are currently recruiting**. If patients only meet the criteria for 1 currently recruiting module, they will be allocated to that module without randomization taking place**.

If a patient withdraws from the study, then his enrollment/randomization code cannot be reused. Withdrawn patients will not be replaced; however, any patient that is withdrawn and is not evaluable may be replaced to ensure a minimum number of evaluable patients.

6.4 Treatment compliance

Treatment compliance will be assured by site reconciliation of study treatment dispensed.

It is the investigator's/institution's responsibility to establish a system for handling study treatments, including investigational products, to ensure that:

- Deliveries of such products from AstraZeneca or its representative are correctly received by a responsible person.
- Such deliveries are recorded.
- Study treatments are handled and stored safely and properly as stated on the label.
- Study treatments are only dispensed to study patients in accordance with the protocol.

At the end of the study, it must be possible to reconcile delivery records with records of usage and destroyed/returned stock.

Any change from the dosing schedule, dose interruptions, dose reductions, and dose discontinuations should be recorded in the electronic case report form (eCRF).

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

The study personnel at the investigational site will account for all drugs dispensed and for appropriate destruction. Certificates of delivery and destruction should be signed. The study monitor will check these records to confirm the compliance with the protocol administration schedule.

Please refer to the module describing the patient's study treatment for more information on treatment compliance.

6.5 Treatment assignment

6.5.1 Methods for assigning treatment groups

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

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

The Investigator(s) will:

1 Obtain signed informed consent from the potential subject before any study-specific procedures are performed.

2 Assign potential subject a unique enrollment number (i.e., E-code) using IWRS. The E-code is sequentially issued and will be used to identify the subject on all study-related documents including the eCRF.

3 Determine subject eligibility. See Sections 5.1 and 5.2.

4 Declare if subject has soft tissue measurable disease by RECIST v1.1 or bone only disease using the IWRS.

5 Assign eligible subject to a module.

When feasible, allocation or randomization will be done centrally via IWRS after subject eligibility is established and prior to treatment. Every effort should be made to minimize the time between allocation or randomization and starting the study drug. It is recommended that subjects commence study drug as soon as possible after allocation or randomization.

If the subject is found to be ineligible during screening, the subject 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 subject withdraws from participation in the study, then his assigned codes cannot be reused.

6.5.2 Procedures for handling incorrectly allocated patients

Subjects who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Subjects who are enrolled, but subsequently found not to meet all the eligibility criteria must not be assigned into a module or initiated on treatment, and must be withdrawn from the study. Where a subject does not meet all the eligibility criteria but is assigned into a module in error, or incorrectly started on treatment, the Investigator should inform the Medical Monitor immediately, and a discussion should occur between the Medical Monitor and the Investigator regarding whether to continue or discontinue the subject from treatment. All decisions must be appropriately documented.

6.6 Concomitant therapy

The following treatments and the medications listed in Appendix J are prohibited or are to be used with caution while patients are receiving AZD4635. Details for other study treatments are provided in the modular-specific appendix.

Table 5 Restricted medications

Medication/class of drug:	Usage (including limits for duration permitted and special situations in which it is allowed):
CYP1A2 inhibitors or inducers.	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 J for a list of the prohibited medications.

Table 6 Prohibited medications

Prohibited medication/class of drug:	Additional Information
No other investigational therapy should be given to patients. No anticancer agents other than the study medications should be given to patients.	If such agents are required for a patient, then the patient 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 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.	Use of potent inhibitors or inducers of BCRP and sensitive substrates of OATP1B1/3, OAT1, OCT1, OCT2, MATE1 and P-gp is therefore prohibited in the current study (see Appendix J).
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), ginkgo biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng.	Patients 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 in advance.

6.6.1 COVD-19 Vaccination Guidance

Authorized/approved COVID-19 vaccines can be given to patients in this study. Investigators should follow the Clinical Study Protocol and their local prescribing information and policies when considering if vaccination against COVID-19 is appropriate for their patients.

If you are considering vaccinating your patient against COVID-19, please consider the following:

- For a specific vaccine, consider the potential impact of its relevant labeling information (i.e., "Indications," "Contraindications," "Warnings and Precautions," "Adverse Reactions") on its use in the study population and individual subject.
- Please contact the manufacturer of theCOVID-19 vaccine if you have any questions concerning their product.

To better assess the overall impact of COVID-19 vaccination on a particular study and study population, ensure that both the COVID-19 vaccination details (including brand name and manufacturer) is captured in eCRF as concomitant medication, and adverse reactions are reported.

6.6.2 Additional concomitant treatment

- Pre-medication will not be required, but may be utilized following the first doses of the investigational products. This includes management of nausea, diarrhea, and vomiting. If a patient has a known history of nausea and vomiting with prior therapy, it is strongly recommended that prophylactic anti-emetics be initiated at the start of treatment (see Section 8.4.5.2).
- Blood and blood product transfusions, including platelet infusions, are allowed at any time during the study, except to meet inclusion criteria.
- Patients already taking erythropoietin at the time of screening for the study may continue it provided they have been taking it for more than one month at the time study treatment is started.
- Granulocyte colony stimulating factors (GCSFs) are permitted for use at the discretion of the Investigator.
- Patients should avoid corticosteroids during the study. If treatment with corticosteroids is indicated, the Investigator should discuss with the Medical Monitor. If in the interest of patient safety the Investigator must treat the patient immediately and a discussion is not feasible, the Medical Monitor should be notified in writing.
- Patients may receive treatment with bisphosphonates or denosumab for the treatment of bone metastases.
- Patients should avoid medications or drugs that increase risk for seizure (e.g., tricyclic antidepressants, pseudoephedrine, anesthetics, amphetamines, cocaine).
- Patients may receive treatment with megestrol acetate when prescribed for appetite stimulation.
- Patients may take low molecular weight heparin. It is recommended that patients treated with an anticoagulant should have their anticoagulation monitored carefully and dose adjusted accordingly.

6.6.3 Other concomitant treatment

Other medication than that described above, which is considered necessary for the patient's safety and wellbeing, may be given at the discretion of the Investigator and recorded in the appropriate sections of the eCRF.

6.7 Dose modification

Please refer to each modular-specific appendix for details on dose reduction.

Management of AZD4635-related toxicities and related dose modifications can be found in Section 8.4.5.

6.8 Treatment after the end of the study

After this study primary DCO, the clinical study database will be closed to the entry of new data. Patients receiving their assigned study treatment at the time of the primary DCO will be

able to continue to receive study treatment if, in the opinion of the Investigator, they are still deriving clinical benefit.

Patients who remain on study treatment after the primary DCO will be managed by the Investigator according to routine clinical practice if not specified differently in the study modules. It is generally recommended to continue observing ongoing patients at the frequency indicated within the study plans as described in the SoA, however the assessments are at the Investigators' discretion based on the individual case. Restrictions regarding concomitant medications (Section 6.6) will be followed while the patient is receiving the IP(s). Study treatment will be supplied to sites outside of the IWRS. Drug dispensation and reconciliation will be performed by the site on each patient visit. Serious adverse events, overdose and pregnancy will be reported after the last dose of study treatment, for the duration stated in the relevant module, using a paper form.

Study will be open until last patient treated. Final Last Subject Last Visit will be defined as last patient's treatment discontinuation.

If study drug is approved on market for use in disease under study indication, patients may be discontinued and switched to marketed product. Drug supply options can be available depending on the country and will be proposed to patient when found as best way to continue treatment by both AZ and investigator.

7 DISCONTINUATION OF TREATMENT AND PATIENT WITHDRAWAL

7.1 Discontinuation of study treatment

Patients that discontinue 1 study drug may remain on the study and receive other study drug(s) as long as they are continuing to derive clinical benefit (see Section 8.4.6). Patients may be discontinued from study drug(s) in the following situations:

- Patient decision. The patient is at any time free to discontinue treatment, 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 drug(s).
- Investigator decision or severe non-compliance with the Clinical Study Protocol
- Confirmed disease progression unless, in the opinion of the Investigator, the patient is still receiving clinical benefit. Patients will continue study treatment until objective disease progression, or beyond RECIST 1.1 defined progression if patient is receiving clinical benefit, as judged by the Investigator and in the absence of discontinuation criteria. Tumor assessment must continue while patient continues to receive study treatment as per Section 8.1.1.

- Patients incorrectly initiated on study drug(s) (e.g., patient is determined to have met one or more of the exclusion criteria for study participation at study entry and continuing investigational therapy might constitute a safety risk)
- Patient started alternative anticancer therapy including another investigational agent
- Patient lost to follow-up

Note that discontinuation from study treatment is NOT the same thing as a complete withdrawal from the study.

See the SoA of the assigned module for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed. The reason for study drug and combinational agent discontinuation will be recorded in the eCRF.

7.1.1 Procedures for discontinuation of study treatment

The Investigator should instruct the patient to contact the site before or at the time if study treatment is stopped. Discontinuation of study treatment, for any reason, does not impact the patient´s participation in the study. A patient that decides to discontinue study treatment will always be asked about the reason(s) and the presence of any AEs. The date of last intake of study treatment and the combinational agent should be documented in the eCRF. All study treatment should be returned by the patient at his next on-site study visit or unscheduled visit. Patients permanently discontinuing study treatment should be given locally available standard of care therapy, at the discretion of the Investigator.

The patient should continue attending subsequent study visits and data collection should continue according to the study protocol. If the patient 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 patient, a contact with a relative or treating physician, and/or information from medical records. The approach taken should be recorded in the medical records. A patient who agrees to modified follow-up is not considered to have withdrawn consent or to have withdrawn from the study.

7.1.2 Procedures for patients who test positive for COVID-19

During the study, COVID-19 tests may be prescribed, if required, and in accordance with local guidance. If a patient tests positive, their continued participation in the study and their treatment with the study drugs will be discussed with the Medical Monitor.

7.2 Lost to follow-up

A patient will be considered potentially lost to follow-up if he fails to return for scheduled visits and does not reply to contact attempts by site personnel.

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

- Site personnel must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule.
- Before a patient is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the patient or next of kin (e.g. repeat telephone calls, certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Efforts to reach the patient should continue until the end of the study. Should the patient be unreachable at the end of the study, the patient should be considered to be lost to follow-up with unknown vital status at end of study and censored at latest follow-up contact.

7.3 Withdrawal from the study

A patient may withdraw from the study (e.g., withdraw consent) at any time (study drug(s) **and** assessments) at his own request, without prejudice to further treatment. The reason for patient withdrawal will be recorded in the eCRF.

If a patient decides to withdraw from the study, including study treatment, the investigator needs to confirm whether the patient:

- Withdraws consent to all further participation in the study including any further follow up (e.g., survival contact telephone calls)

OR

- Withdraws consent from study treatment, but agrees to follow-up procedures (as defined in Section 7.1).

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

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

If a patient withdraws consent to the use of mandatory biological samples, the samples will be disposed of/destroyed if possible and the action documented. If samples have already been analyzed, the sponsor is not required to destroy the results of this research.

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

In the event that the patient has actively withdrawn consent to the processing of his personal data, the vital status of the patient can be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws

See the SoA in the relevant module for data to be collected at the time of study drug discontinuation and follow-up and for any further evaluations that need to be completed. All study drug should be returned by the patient.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the core SoA. For all assessments after screening, see the module-specific SoA.

The Investigator will ensure that data are recorded on the eCRF as specified in this clinical study protocol and in accordance with the instructions provided. The Medidata Rave electronic data capture (EDC) system will be used for data collection and query handling.

The Investigator will ensure the accuracy, completeness, and timeliness of the data recorded and the provision of answers to data queries according to the Clinical Study Agreement. The Investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue study treatment.

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 patients meet all eligibility criteria. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the patient's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized 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 number of samples taken, as well as the volume required for each analysis, may be changed during the study as emerging data become available. However, the estimated total volume of blood that will be drawn from each patient in this study during screening and the

first cycle of treatment will not exceed 300 mL (over a 1-month period). Any additional requirements are specified within the module.

8.1 Efficacy assessments

All patients are expected to have both CT/MRI/PET and bone scans at each scheduled disease assessment. Evaluation of objective tumor response in this study will be done using RECIST v1.1 Criteria in evaluable soft tissue disease (see Appendix G). Tumors will be assessed at screening according to the module-specific SoA. Reassessment of tumors will be done by the same methods used to establish baseline tumor measurements.

PCWG3 PSA criteria (Appendix I) will also be used to evaluate response and progression. These criteria will be followed for determining the change in PSA levels. Prostate-specific antigen (PSA) levels in this study will be measured at screening, at the start of each new treatment cycle, at the end of study visit, at any other timepoints 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 PCWG-3 (Table 7)
- Death

Patients with PSA progression are permitted and encouraged to continue treatment until symptomatic or 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.

All CT/bone scans and all imaging assessments performed for RECIST 1.1 tumour assessment will be reviewed at site. Duplicates must be available at the site in readiness to be sent for retrospective independent central RECIST 1.1 review, if deemed appropriate. More information on this procedure is available in the Image Acquisition Guideline for this study.

8.1.1 Tumor assessments with RECIST v1.1

RECIST version 1.1 guidelines for measurable and non-measurable target lesions (TLs) and non-target lesions (NTLs) and the objective tumor response criteria are presented in Appendix G.

Baseline tumor 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 patients. 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.

The first follow-up assessment should be initially at 6 weeks (±1 week) following the start of AZD4635 dosing and subsequent assessments will be performed every 2 cycles (every 8 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 patient has not progressed, every attempt should be made to perform subsequent assessments at the scheduled visits.

Categorization of objective tumor response assessment will be based on the RECIST Version 1.1 guidelines for response of soft tissue lesions: CR (complete response), PR (partial response), SD (stable disease), and PD (progression of disease). For patients who only have non-measurable TLs at baseline, categorization of objective tumor response assessment will be based on the RECIST Version 1.1 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 patient'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 in target disease, the overall tumor 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 tumor response variables

At each visit, patients will be programmatically assigned a RECIST visit response of CR, PR, SD 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 tumor burden was at a minimum (i.e., smallest sum of diameters previously recorded on study, nadir). In the absence of progression, tumor response (CR, PR, SD) will be calculated in comparison to the baseline tumor measurements obtained before starting treatment.

If a patient has had a tumor assessment that cannot be evaluated, then the patient will be assigned a visit response of NE, unless there is evidence of progression in which case the response will be assigned as PD.

For TL measurements, if ≤1/3 of the TL sizes are missing then a scaling-up rule will be applied as follows:

1. If ≤1/3 of lesions recorded at baseline are missing then the results will be scaled up (based on the nadir sizes) to give an estimated sum of diameters and this will be used in calculations (this is equivalent to comparing the visit sum of diameters of the non-missing lesions to the nadir sum of diameters excluding the lesions that are missing and determining at what rate the lesions are changing).

2. If >1/3 of lesions recorded at baseline are missing then the TL response will be NE. However, if the sum of non-missing TL diameters would result in PD (i.e., if using a value of 0 for missing lesions the sum of diameters has still increased by >20% or more compared to the smallest sum of diameters on study), PD takes precedence over NE.

3. A visit response of CR will not be allowed if any of the TL data are missing.

Objective response rate is defined as the proportion of patients with measurable disease at baseline who have a confirmed ORR per RECIST v1.1. For the analysis of objective response rate an "evaluable-for-response" population will be derived and will exclude patients 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 <10mm 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 (patients 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 patient 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 tumor size will be determined for patients with measurable disease at baseline and is derived at each visit by the percentage change in the sum of the diameters of TLs.

For further details see Appendix G of this CSP.

CCI [redacted]

CCI [redacted]

It is important to follow the assessment schedule as closely as possible. Please refer to the Study Plan in each module and Appendix G.

8.1.2 PCWG3 bone lesions assessment

Categorization of tumor progression of bone lesions will be based on the PCWG-3 criteria. Bone lesions will be assessed by bone scintigraphy commonly performed with Technetium-99 (bone scans) or PET scan. 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 Appendix G).

The requirements for determination and confirmation of radiographic progression by either bone scan (bone progression) or CT/MRI (soft tissue progression) are summarized in Table 7.

Table 7 Requirements for documentation of progression

Visit Date	Criteria for Bone Progression	Criteria for Soft Tissue Progression
First visit after baseline (expected at week 6 after the start of AZD4635 study treatment)	• 2 or more new lesions compared to baseline bone scan. • Requires confirmation at least 6 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 4 weeks (but no more than 8 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 6 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.

8.1.3 CCI [redacted]

CCI [redacted]

8.1.4 PWCG3 PSA criteria

All patients should have PSA collected [redacted] at screening, at the start of each new treatment cycle, at the end of study treatment, and as indicated in the SoA of each module. PSA [redacted] should also be collected when clinically indicated as per Investigator discretion.

PWCG3 PSA criteria are located in Appendix I.

8.2 Safety assessments

Planned time points for all safety assessments are provided in the module-specific SoA.

8.2.1 Clinical safety laboratory assessments

See Table 8 for the list of clinical safety laboratory tests to be performed and the screening and module-specific SoA 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 center as source data for laboratory variables.

For information on how AEs based on laboratory tests should be recorded and reported, see Section 8.3.7.

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date, time of collection and results (values, units and reference ranges) will be recorded on the appropriate eCRF.

Safety laboratory assessments will be performed locally at each study site laboratory by means of their established methods. Therefore, the number of samples/blood volumes is subject to site-specific change.

Laboratory values that meet the criteria for CTCAE Grade 3 or have changed significantly from baseline and are considered to be of clinical concern will be repeated/confirmed within 7 days and followed up as appropriate.

Table 8 Laboratory safety variables

Hematology	**Clinical chemistry**
Blood (B)-Hemoglobin	Albumin
B-Leukocyte	Alkaline phosphatase[b]
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]
B-Platelet count	Creatinine[d],[e]
	Gamma glutamyltransferase (GGT)[d]
Coagulation	Glucose
Prothrombin Time	Lactate dehydrogenase (LDH)
Or	Lipase[c]
International normalization ratio (INR) and activated partial thromboplastin time (aPTT)	Magnesium[d]
	Phosphate
Urinalysis	Potassium
Bilirubin, blood, color and appearance, glucose, ketones, pH, protein, and specific gravity	Sodium
	Total bilirubin[b]
Additional Tests	Total protein
Testosterone	Thyroid stimulating hormone[f]
Prostate specific antigen (PSA)	Free T4[g]
Hepatitis A, hepatitis B surface antigen, hepatitis C antibody, and HIV antibody[h, i, j,k]	Free T3[g]
CCI [redacted]	Urea nitrogen
	Uric acid
	C-reactive protein (CRP)

[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] If TSH is measured within 14 days prior to Day 1 (first infusion day), it does not need to be repeated at Day 1.

[g] 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.

[h] Hepatitis A testing will only be performed if the patient is considered symptomatic per the Investigator.

[i] Hepatitis B testing: hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody, IgM hepatitis B core antibody. If hepatitis B core (total) antibody testing is unavailable, then the hepatitis B core IgG and IgM should both be obtained instead. If a test is not locally available, then standard local practice for assessing hepatitis B status should be utilized. If screening tests are positive, a HBV-DNA test should be obtained to assess infection status.

[j] Hepatitis C antibody. If screening antibody is positive, an HCV-RNA test should be performed to assess infection status.

[k] Human immunodeficiency virus-1 antibody

Note: In case a patient shows an AST **or** ALT ≥3xULN together with TBL ≥2xULN please refer to Appendix E "Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law" for further instructions.

8.2.2 Physical examinations

A complete physical examination will be performed and include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculo-skeletal (including spine and extremities) and neurological systems.

Physical examination will be performed at visits as specified in the module-specific SoA. Investigators should pay special attention to clinical signs related to previous serious illnesses. New or worsening abnormalities may qualify as AEs (see Section 8.3.7 for details).

Significant abnormal findings will be recorded in the Medical History or as an AE. Abbreviated symptom-directed physical examinations will be conducted at subsequent visits post-dosing.

8.2.3 Performance status

Performance status will be assessed as indicated in the Study Plan figures according to ECOG criteria as follows:

0 = Fully active, able to carry out all pre-disease activities without restrictions

1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g., light housework, 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 self-care, totally confined to bed or chair.

8.2.4 Vital signs

Vital signs (pulse rate, systolic and diastolic BP, respiration rate, and temperature) will be assessed according to the screening and module-specific SoA. Body weight is also recorded at each visit and height is recorded at screening.

- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 10 minutes of rest for the patient in a quiet setting without distractions (e.g., television, cell phones).
- For the baseline BP measurement, 2 or more readings should be taken at 2-minute intervals and averaged. If the first 2 diastolic readings differ by more than 5 mmHg, then an additional reading should be obtained. For all other subsequent measurements, institutional standards for measuring vital signs should be followed.

If antihypertensive management is initiated during the study, more frequent BP monitoring should be initiated until a stable antihypertensive regimen has been established.

Additional assessments may be performed at the discretion of the Investigator, if clinically indicated.

8.2.5 Electrocardiograms

Electrocardiograms (ECGs) will be obtained at screening, end of treatment, and when clinically indicated.

Resting 12-lead ECG

Twelve-lead ECGs will be obtained after the patient has been resting supine for at least 10 minutes prior at times indicated in the screening and module-specific SoA. All ECGs should be recorded with the patient in the same physical position.

For each time point 3 ECG recordings should be taken about a minute apart within a 5-minute window per timepoint. A standardized ECG machine should be used and the patient should be examined using the same machine throughout the study, when feasible.

The ECG traces will be recorded and reviewed as per the study-specific ECG manual. The Investigator or designated physician will review each of the ECGs and may refer the patient 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 an AE (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 on the eCRF.

8.2.6 Echocardiography or multi-gated acquisition scan

An echocardiogram (ECHO) should be performed at screening (≤14 days prior to Cycle 1 Day 1) and within 14 days after a clinically significant ECG finding (T wave inversion/flattening). If an ECHO cannot be taken, a cardiac MRI or multigated acquisition (MUGA) scan to assess left ventricular ejection fraction will be conducted. In case of any T wave abnormality, the ECHO, MRI, or MUGA should be repeated at the end of treatment (EOT) visit to address the question of recovery during the off-treatment period.

8.2.7 End-of-treatment visit

Patients will return to the clinic for an EOT visit that is to be performed as soon after the study drug is stopped as possible, preferably within 2 days of stopping drug. For patients who have had drug held prior to the decision for discontinuation, the EOT visit should be performed within 7 days of the decision. Tumor assessments will be done at this visit, if they have not been performed within the past 2 months. Other assessments to be performed are presented in the SoA in the modular-specific appendix.

8.2.8 Follow-up visits

8.2.8.1 30-day follow-up visit

A safety follow-up visit will be performed approximately 30 (±7) days after the study drug(s) is (are) permanently discontinued, unless the patient withdraws consent. The primary purpose of this visit is to follow up on any AEs ongoing at the time of study treatment 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 treatment discontinuation, or any new events within 30 days of last study treatment unless otherwise indicated in the specific module, 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.

8.2.8.2 Progression-free follow-up visits

Patients who discontinue study treatment prior to the occurrence of objective PD will be followed with PSA samples and CT/MRI/PET and bone scans every 3 months (±1 week) from the last date of the last tumor response assessment until either: objective PD has been confirmed, withdrawal of consent, until the primary analysis DCO, or until the study or module is terminated by the Sponsor.

8.2.8.3 Survival follow-up

Patients will be followed every 3 months after the last dose of study drug for survival until withdrawal of consent, or until the primary DCO for the study. The survival and subsequent cancer therapy follow-up can be done by a medical record review or telephone call at the Investigator's discretion.

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.

8.2.9 COVID-19 Testing

Tests for active COVID-19 infection may be prescribed, where appropriate, and in accordance with local procedures. If a patient tests positive, their continued participation in the study and treatment with the study drugs will be discussed with the Medical Monitor

8.3 Collection of adverse events

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

The definitions of AEs and SAEs can be found in Appendix B.

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

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. For information on how to follow up AEs see Section 8.3.3.

8.3.1 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

8.3.2 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 follow-up period, unless specified differently in each module (see module-specific guidance).

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix B. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs in former study patients. However, if the Investigator learns of any SAE, including a death, at any time after a patient's last visit and he/she considers the event to be reasonably related to the study treatment or study participation, the Investigator may notify the Sponsor.

The methods of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix B.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each patient at subsequent visits/contacts. All SAEs/non-serious AEs/AEs of special interest (AESIs) (see module-specific guidance) will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up

Any AEs that are unresolved at the patient'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 eCRF. AstraZeneca retains the right to request additional information for any patient with ongoing AEs/SAEs at the end of the study, if judged necessary.

8.3.4 Adverse event data collection

The following variables will be collected for each AE:

- AE (verbatim)

- The date when the AE started and stopped
- CTCAE 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 which criterion
- Date of hospitalization
- 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

8.3.5 Causality collection

The Investigator will 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 related to the IP?"

For SAEs, causal relationship will 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 Clinical Study Protocol.

8.3.6 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study site staff: "Have you had any health problems since the previous visit?", 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.

8.3.7 Adverse events based on examinations and tests

The results from the protocol mandated laboratory tests and vital signs will be summarized in the clinical study report (CSR). Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs, ECGs, or other safety assessments should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the IP.

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 will use the clinical rather than the laboratory term (e.g., anemia versus low hemoglobin 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 (see Sections 8.3.9 and 8.3.10).

8.3.8 Hy's law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥3xULN together with TBL ≥2xULN 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.

8.3.9 Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the IP 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.

8.3.10 New cancers

The development of a new cancer should be regarded as an SAE. New cancers are those that are not the primary reason for the administration of the study treatment and have been

identified after the patient's inclusion in this study. They do not include metastases of the original cancer.

8.3.11 Deaths

All deaths that occur during the study, or within the follow-up period after the administration of the last dose of study drug, should be reported as follows:

- Death clearly resulting from disease progression should be communicated to the study monitor at the next monitoring visit and should be documented in the eCRF on the Death page. It should not be reported as an SAE.
- When death is not clearly due to PD of the disease under study, the AE causing the death should be reported to the study monitor as an SAE within 24 hours. It should also be documented on the Death page in the eCRF. The report should contain a comment regarding the co-involvement of PD, if appropriate, and should assign a single primary cause of death together with any contributory causes
- Deaths with an unknown cause should always be reported as SAEs, but every effort should be made to establish a cause of death. It should also be documented in the Statement of Death page in the eCRF. A post-mortem may be helpful in the assessment of the cause of death, and if performed a copy of the post-mortem results (with translation of important parts into English) should be forwarded to an AstraZeneca representative within the usual time frames.

Deaths occurring after the protocol defined safety follow-up period after the administration of the last dose of study drug should be documented on the Death page. If the death occurred as a result of an event that started after the defined safety follow-up period and the event is considered to be due to a late onset toxicity to study drug, then it should also be reported as an SAE.

8.3.12 Adverse events of special interest

An AESI is one of scientific and medical interest specific to understanding of the IP and may require close monitoring and rapid communication by the Investigator to the Sponsor, or delegate. 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 IP.

Please refer to the modular-specific appendices for AESIs to be followed.

8.3.13 Safety data to be collected following the primary DCO of the study

For patients continuing to receive treatment after primary DCO and database closure, it is recommended that the patients continue the scheduled site visits and Investigators monitor the patient's safety laboratory results prior to and periodically during treatment in order to manage AEs in accordance with the Dose Modification and Toxicity Management Guidelines (see

Section 8.4.5). All data after the primary DCO and database closure will be recorded in the patient notes but, with the exception of SAEs, will not otherwise be reported for the purposes of this study.

All SAEs that occur in patients still receiving treatment (or within the 90 days following the last dose of treatment) after the primary DCO and database closure must be reported as detailed in Section 8.4.1.

8.4 Safety reporting and medical management

8.4.1 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the IP, 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 will inform the appropriate AstraZeneca representatives within one day i.e., immediately but **no later than 24 hours** of when he or she becomes 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.

SAE information will be sent via secure e-mail connection or via fax. The Innovations Safety Department standard paper SAE Report Form, with supporting relevant source documents (e.g., history and physical [H&P], hospital discharge summary, autopsy report when available, results of relevant diagnostic tests completed to evaluate the event), will be attached and sent via:

- Secure email (Innovations SAE mailbox: PPD

or

- Fax (Innovations safety fax number): PPD

Transmission of the SAE Report Form should be confirmed by the site personnel submitting the report.

Follow-up information for SAEs and information on non-serious AEs that become serious should also be reported to Innovations Safety Department as soon as it is available; these reports should be submitted using the Innovations SAE Report Form. The detailed SAE reporting process will be provided to the sites in the SAE reporting guidelines contained in the study reference manual. The Innovations Medical Monitor works with the Investigator to ensure that all the necessary information is provided to the Innovations Safety Department

within 1 calendar day of initial receipt of the information for fatal and life-threatening events and **within 5 calendar days** of initial receipt of the information for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel will 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 he or she becomes aware of it.

Investigators must report SAEs and follow-up information to their responsible IRB according to the policies of the responsible IRB. For fatal or life-threatening AEs for which important or relevant information is missing, active follow-up is undertaken immediately.

AstraZeneca, or their representatives, will provide Regulatory Authorities, Ethics Committees, and Principal Investigators with clinical safety updates/reports according to local requirements.

Full details of the AE reporting process are provided in the Safety Handling Plan for the study.

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

8.4.2 Pregnancy

Conception must be avoided during paternal exposure to AZD4635. If a pregnancy in the female partner of a male patient is reported, the investigator should inform the Innovations Safety Department within 24 hours of learning of the pregnancy. Exception to this is if the pregnancy is discovered before the study subject has received any study drug. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.4.2.1 Paternal exposure to AZD4635

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

Pregnancy of a patient's partner is not considered to be an AE. However, outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the first date of dosing until 3 months (unless specified differently in relevant module) after dosing should, if possible, be followed up and documented.

Male patients should use condoms with female partners during the study and for 12 weeks (3 months or as specified in relevant module) after the last dose of AZD4635, 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 patients with a desire to have children. See relevant module for module-specific information.

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

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

8.4.3 Overdose

Any dose of AZD4635 in excess of 110% of the dose per cycle of treatment specified according to the protocol will constitute an overdose, unless associated with an AE, in which case 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. Please refer to relevant module to see module-specific overdose guidance.

- 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 of an AstraZeneca study drug occurs in the course of the study, then the Investigator or other site personnel will inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes 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.

- For overdoses associated with a SAE, the standard reporting timelines apply (see Section 8.3.2). For other overdoses, reporting must occur within 30 days.

8.4.4 Medication error

If an medication error occurs in the course of the study, then the Investigator or other site personnel will inform the appropriate AstraZeneca representatives within 1 day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within 1 calendar day (initial fatal/life-threatening or follow-up fatal/life-threatening) or 5 calendar days (other serious initial and follow-up) if there is an SAE associated with the medication error (see Section 8.3.2) and within 30 days for all other medication errors.

The definition of a medication error can be found in Appendix B.

8.4.5 Management of AZD4635-related toxicities

AZD4635 management and discontinuation guidelines for non-hematologic toxicities (except hypertension) are shown in Table 9. Intrapatient dose re-escalation is not permitted. AZD4635 dose reduction guidelines are in Section 6 of the study-specific modules.

If a patient 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 reduced and supportive therapy administered, as required. If the toxicity resolves or reverts to ≤ CTCAE Grade 2 within 2 treatment weeks and the patient is showing clinical benefit per the Investigator, treatment with AZD4635 may be restarted. If the toxicity does not resolve to ≤ CTCAE Grade 2 after 2 weeks of treatment then the patient should be withdrawn from the study and observed until resolution of the toxicity. Maximum drug holiday allowed is 2 weeks for non-immune-mediated toxicity.

Table 9 AZD4635 dose modifications and discontinuation criteria for non-hematologic toxicities (except hypertension)

NCI CTCAE 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 Toxicity remains Grade 3 to 4 or is clinically significant[a] >14 days	Restart AZD4635 at 1 dose level reduction Discontinue AZD4635
Recurrence of Grade 3	Reduce 1 more dose level if module-specific guidance allows 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%), increases 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), QTc prolongation >500 ms.

8.4.5.1 Hypertension

Treatment of hypertension and goal BP will be in accordance with international guidelines. AZD4635 dose reduction and discontinuation guidelines for the management of hypertension are shown in Table 10. Details on daily management of BP are provided in Section 8.2.4.

Patients taking antihypertensive medications will take and record BP readings twice daily while at home (recommended 1 hour post-dose) for at least the first 3 weeks after starting study drug. Twice-daily monitoring should be re-implemented after any AZD4635 hold/dosing delay for 2 weeks or until the patient is re-established on a stable anti-hypertensive regimen, whichever takes longer. Patient BP readings should be reviewed with the study team on a weekly basis for the first 3 weeks of study treatment to ensure that BP guidelines are being correctly followed.

Table 10 AZD4635 dose modifications and discontinuation criteria for management of hypertension

Event severity	Antihypertensive therapy	BP monitoring	AZD4635 dose modification
Systolic BP 150 to 159 mm Hg or diastolic BP 90 to 99 mm Hg; medical intervention indicated; recurrent or persistent (≥24 hrs); symptomatic increase by >20 mm Hg (diastolic) or to >150/90 mm Hg if previously within normal limits	Initiate/escalate antihypertensive medication as per local guidelines. BP goal and the choice of the antihypertensive drug will be individualized for each patient.	Increase frequency of monitoring until stabilized to BP <150/90 mmHg	None

Event severity	Antihypertensive therapy	BP monitoring	AZD4635 dose modification
Grade 3 (systolic BP >=160 mm Hg or diastolic BP >=100 mm Hg); medical intervention indicated; more than one drug or more intensive therapy than previously used indicated	Initiate or maximize BP therapy as per local guidelines. Consider consult with a BP management specialist	Increase frequency of monitoring until stabilized to BP <150/90 mmHg	May continue AZD4635 with optimization of antihypertensive management unless persistent BP-related clinical symptoms. Hold AZD4635 if BP is not decreased to grade 2 within 48 hours after optimum therapy is instituted. If BP is reduced to baseline or Grade 1 within 14 days and considered stable, AZD4635 may be resumed at original dose. Discontinue AZD4635 if BP does not resolve to Grade 1 within 14 days. Discontinue AZD4635 if BP systolic ≥180 mmHg and/or diastolic ≥110 mmHg) Recurrence of Grade 3: Discontinue study drug.
Grade 4 Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated	Initiate treatment per local guidelines, including hospitalization, ICU management, and IV therapy as necessary		Discontinue AZD4635

8.4.5.2 Nausea and vomiting

If a patient has a known history of nausea and vomiting with prior therapy, it is strongly recommended that prophylactic anti-emetics be initiated at the start of treatment. They should continue as required thereafter, in accordance with local treatment practice guidelines. Additionally, AZD4635 capsules can be taken with a light meal/snack which may improve tolerability (i.e., 2 pieces of toast or a couple of biscuits).

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).

8.4.6 Duration of therapy

Patients may continue to receive AZD4635 and/or other combination therapeutic agent as long as they are continuing to show clinical benefit, as judged by the Investigator, and in the absence of discontinuation criteria.

8.5 Pharmacokinetics

Venous blood samples (2mL each) for determination of concentrations of AZD4635 and its metabolites in plasma will be taken in this study for all modules.

Please refer to the module-specific appendix for AZD4635 collection time points.

8.5.1 Determination of drug concentration

Samples for determination of drug concentration in plasma will be analyzed by analytical test sites on behalf of AstraZeneca, using an appropriate bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

All samples still within the known stability of the analytes of interest at the time of receipt by the bioanalytical laboratory will be analyzed.

In addition, the PK samples may be subjected to further analyses in order to further investigate the presence and/or identity of drug metabolites. Any results from such analyses will be reported separately from the CSR, but known metabolites will be reported in the CSR.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the CSR but separately in a Bioanalytical Report.

8.5.2 Storage and destruction of pharmacokinetic samples

Pharmacokinetic (PK) samples will be disposed of after the bioanalytical report finalization or 6 months after issuance of the draft bioanalytical report (whichever is earlier), unless requested for future analyses.

Pharmacokinetic samples may be disposed of or anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

8.6 CCI [redacted]

CCI [redacted]

8.7 CCI

8.7.1 CCI

CCI

8.7.2 CCI

CCI

8.8 CCI

CCI

8.8.1 CCI

8.8.1.1 CCI

CCI

8.8.2 CCI

CCI

8.8.3 CCI

CCI [redacted]

8.8.4 CCI

CCI [redacted]

8.8.5 CCI

CCI [redacted]

8.9 Medical Resource Utilization and Health Economics

Medical resource utilization and health economics are not evaluated in this study.

9 STATISTICAL CONSIDERATIONS

A comprehensive statistical analysis plan will be developed and finalized before database lock and will describe the patient populations to be included in the analyses (performed by AstraZeneca and/or a third party), 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 clinical study report.

The primary aim of the study is to assess the efficacy, safety, and tolerability of multiple study drugs in patients with prostate cancer.

9.1 Statistical hypotheses

Not applicable

9.2 Sample size determination

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

The primary efficacy endpoint is PSA decline from baseline measure ≥50% (PSA50) and overall response rate (ORR) per RECIST v1.1. The PSA endpoint will be used to define the sample size for patients with and without measurable disease at baseline.

In Module 1, 2, and 3 (if conducted) there will be approximately 30 PSA evaluable patients in each module, and approximately 20 patients will have RECIST measurable disease at baseline in each module.

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

[redacted]

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

[redacted]

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

9.3 Populations for analyses

For purposes of analysis, the following populations are defined:

Population	Description
Pharmacokinetics	Dosed patients with at least 1 reportable PK concentration
Tumor response	Dosed patients with a baseline tumor assessment, and measurable disease at baseline.
PSA response	Dosed patients with an abnormal baseline PSA data (≥1ng/mL)
Evaluable for efficacy	Dosed patients with a baseline tumor assessment.
Safety analysis set	All patients who received at least 1 dose of study drug

Summaries of PK data for AZD4635 will consider the subset of the PK analysis set with evaluable PK data at that visit for which there are no important AEs or protocol deviations that may impact PK at that visit.

In the case of an important protocol deviation that affects the evaluability of the PK analysis, affected PK data collected will be excluded from the summaries, but will still be reported in the study result listings. Important deviations will be listed and summarized in the CSR.

9.4 Statistical analyses

All analyses will be reported per module.

9.4.1 Definition of endpoints

To meet the objectives for this study, data for the following endpoints will be collected:

- PSA response (Primary)
- Overall Response Rate (Primary)
- AZD4635 and metabolites PK concentrations (Secondary)
- Durvalumab and oleclumab PK concentrations (Secondary)Tumor response (Secondary)
  - DOR
- Overall survival (OS) (Secondary)
- Radiological progression-free survival (rPFS) (Secondary)
- CCI [redacted]
- CCI [redacted]
- Immunogenicity (ADA) (Secondary)
- Safety and Tolerability
  - AEs/SAEs

  - Physical exam and vitals
  - Clinical chemistry/hematology parameters
- CCI [redacted]
- CCI [redacted]

9.4.2 Demographic data

Characteristics of the patients, including medical history and disease characteristics at baseline, will be listed for each patient and summarized by module where appropriate.

9.4.3 Exposure

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

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

Total exposure and total time on study (date of last dose minus date of first dose) will be summarized by the following: mean, standard deviation, minimum, maximum, median and number of observations. In addition, the number and percentage of patients with at least one dose interruption and at least one dose reduction will be presented separately for the initial period of evaluability (defined as 21 days) and for any time following this initial period of the study.

Relative Dose Intensity (RDI) will be calculated, and is defined as follows:

- RDI = 100% * d/D, where d is the actual cumulative dose delivered up to the earlier of progression (or a censoring event) or the actual last day of dosing and D is the intended cumulative dose up to the earlier of progression (or a censoring event) or the actual last day of dosing plus the protocol-defined post-dose rest period.
-

9.4.4 Efficacy analyses

PSA response

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

  - A patient will be regarded as having a single PSA visit response if their PSA level at any post-dose visit is reduced by 50% or more compared with baseline
  - A patient will be regarded as having a confirmed PSA response if they have a reduction in PSA level of 50% or more compared with baseline that is confirmed at

the next assessment at least 3 weeks later (i.e., decrease relative to baseline of at least 50% documented on 2 consecutive occasions at least 3 weeks apart).

PSA progression

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

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

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

Tumor response

Tumor response data will be summarized for dosed patients with measurable disease at baseline and separately for dosed patients that had measurable or non-measurable disease at baseline.

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

Best objective response and ORR will be summarized. Percentage change from baseline in tumor size will be determined for patients 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 by dose level.

Duration of response (DoR) 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.

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

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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 patient withdraws from treatment or receives another anti-cancer therapy prior to progression. Patients who have not progressed (defined as CR, PR or SD by RECIST v1.1 for soft tissue disease, or non-PD for bone disease, see Appendix G) at the time of analysis will be censored at the time of the last evaluable RECIST assessment or bone scan.

However, if the patient progresses or dies after 2 or more missed radiologic visits the patient 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 patients has an assessment for soft tissue disease (MRI/CT) but not for bone disease (bone scan), or vice versa, then this will count as a missed assessment. If the patient has no evaluable post-baseline RECIST v1.1 or bone scan assessment they will be censored at 1 day unless they die within 2 visits of baseline (in which case their date of death will be used).

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 patient will be censored at the latest of the dates contributing to a particular overall visit assessment.

Overall survival

Overall survival is defined as the time from the first dose of AZD4635 until death due to any cause regardless of whether the patient withdraws from study therapy or receives another anti-cancer therapy. Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the subject was known to be alive.

Note: Survival calls will be made in the week following the date of data cut-off (DCO) for the analysis, and if subjects are confirmed to be alive or if the death date is after the DCO date these subjects will be censored at the date of DCO. See Section 7 for methods that can be used to determine status of subjects who withdraw consent or are lost to follow-up.

9.4.5 Safety analyses

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

Data from all cycles of initial treatment will be presented as described in the Statistical Analysis Plan. Adverse events will be listed individually by patient and dose group. For

patients who have a dose modification, all AEs (due to drug or otherwise) will be assigned to the initial dose group. The number of patients experiencing each AE will be summarized by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class, MedDRA preferred term, and CTCAE grade. The number and percentage of patients with AEs in different categories (e.g., causally related, CTCAE Grade ≥3, etc.) will be summarized by dose group, and events in each category will be further summarized by MedDRA system organ class and preferred term, by dose group. Serious AEs will be summarized 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 (see modules for specific time period) after discontinuation of IP will be included in the AE summaries. Any AEs in this period that occur after a patient has received further therapy for cancer (following discontinuation of IP) will be flagged in the data listings. Adverse events occurring after the 30-day or 90-day follow-up period after discontinuation of IP will be listed separately, but not included in the summaries.

Hematology, clinical chemistry, vital signs, ECG data, ECHO/MUGA, demographic data, medical histories, and concomitant medications will be listed individually by patient and suitably summarized. 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 patients.

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.

9.4.6 Other analyses

The analysis of the secondary endpoints PK, known metabolites and immunogenicity will be reported in the CSR. CCI [redacted]

9.4.7 COVID-19 analyses

Refer to the Statistical Analysis Plan for details regarding COVID-19.

9.5 Interim analyses

No formal interim analysis is planned. CCI [redacted]

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11 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 Organizations 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 (e.g., 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 approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

The study will be performed in accordance with the AstraZeneca policy on Bioethics and Human Biological Samples.

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, IRBs, 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 (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB, 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/her representative will explain the nature of the study to the patient or his/her legally authorized representative and answer all questions regarding the study.

Patients must be informed that their participation is voluntary. Patients 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 patient 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.

Patients 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 patient or the patient's legally authorized representative.

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If a patient's partner becomes pregnant during or within 3 months (or as indicated in module-specific appendix) 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.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The Investigator or authorized designee will explain to each patient the objectives of the exploratory research. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. The patient will give a separate agreement to allow any remaining specimens to be used for exploratory research. Patients who decline to participate in this optional research will indicate this in the ICF. If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples already have been analyzed at the time of the request, AstraZeneca will not be obliged to destroy the results of this research.

A 4 Data protection

Each patient will be assigned a unique identifier by the Sponsor. Any patient records or data sets transferred to the Sponsor will contain only the identifier; patient names or any information which would make the patient identifiable will not be transferred.

The patient must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized 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 Patient 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://astrazenecaclinicaltrials.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 patient data relating to the study will be recorded on printed or eCRF unless transmitted to the Sponsor or designee electronically (e.g., 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.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients 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 patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data reported on 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.

Definitions of what constitutes source data can be found in the clinical trial agreement.

A 9 Study and site closure

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. The study may be stopped if, in the

judgment of AstraZeneca, trial subjects are placed at undue risk because of clinically significant findings that:

- meet individual stopping criteria or are otherwise considered significant
- are assessed as causally related to study drug,
- are not considered to be consistent with continuation of the study

Regardless of the reason for termination, all data available for the subject at the time of discontinuation of follow-up must be recorded in the CRF. All reasons for discontinuation of treatment must be documented.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the subjects' interests

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

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 event definitions and additional safety information

B 1 Definition of adverse events

An adverse event (AE) is the development of any untoward medical occurrence in a patient or clinical study patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (e.g. 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 (SAE) is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that fulfills one or more of the following criteria:

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

B 3 Life threatening

'Life-threatening' means that the patient 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 patient's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (e.g., hepatitis that resolved without hepatic failure).

B 4 Hospitalization

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

B 5 Important medical event or medical treatment

Medical and scientific judgment 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, hospitalization, disability or incapacity but may jeopardize the patient 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 judgment 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 (e.g., neutropenia or anemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

B 6 Intensity rating scale:

The grading scales found in the revised National Cancer Institute CTCAE latest version will be utilized 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.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Appendix B 2.

B 7 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 patient 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 etiology 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 recognized 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 limited or insufficient information in the case, it is likely that 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 8 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 drug 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 recognize that could have led to an error

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

- Drug name confusion
- Dispensing error e.g. 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 e.g. tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed e.g. 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) e.g. 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 AZ product

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

Appendix C Handling of Human Biological Samples

C 1 Chain of custody of biological samples

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

The Investigator at each center keeps full traceability of collected biological samples from the patients while in storage at the center until shipment or disposal (where appropriate).

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 documentation of receipt of arrival.

AstraZeneca 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 AZ-assigned biobanks and will be registered by the AstraZeneca Biobank Team during the entire life cycle.

C 2 Withdrawal of Informed Consent for donated biological samples

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

The Investigator:

- Ensures patients' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the signed document returned to the study site
- Ensures that the patient and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organizations holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

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

LABELING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)**. For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and Categories A and B.

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:

- are to be packed and shipped in accordance with IATA Instruction 602.

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, B, C, D, and E viruses, Human immunodeficiency virus types 1 and 2. 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 - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient
- temperature in IATA 650 compliant packaging **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)**
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable
- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging/containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Appendix D CCI

D 1 CCI

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D 2 CCI

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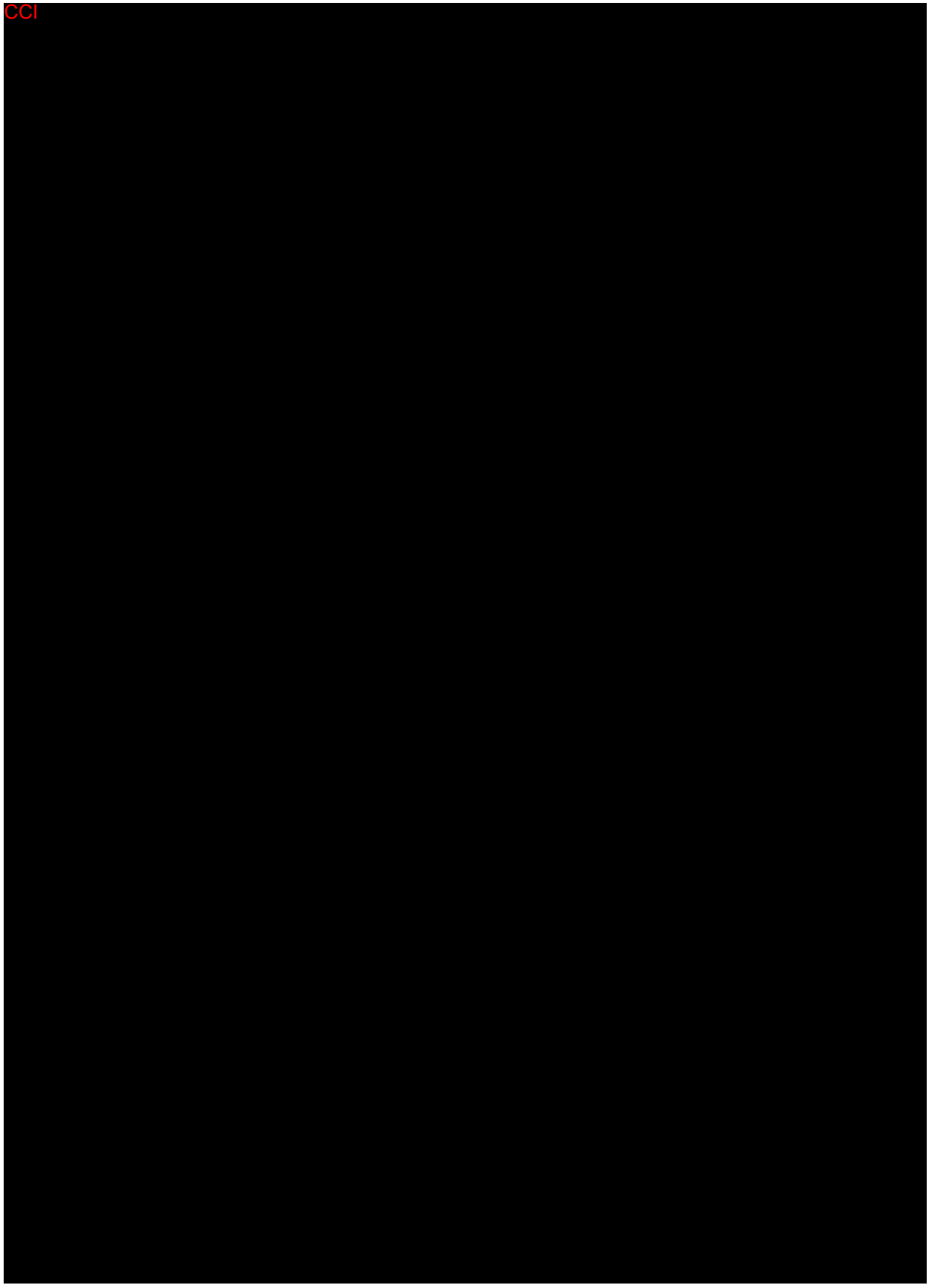

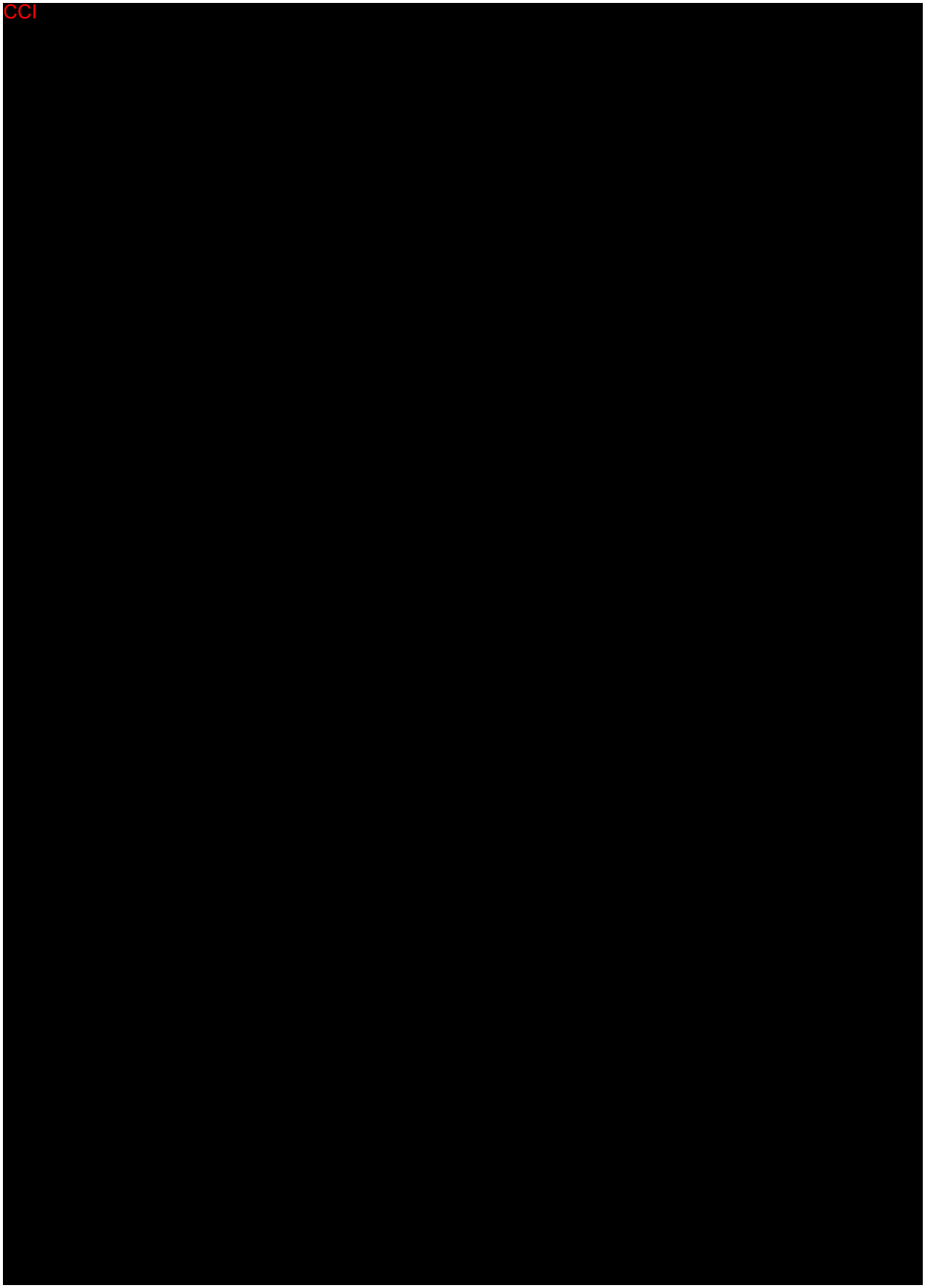
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Appendix E Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law

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 patient meets 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 total bilirubin (TBL) from a local laboratory.

The Investigator will also review Adverse Event (AE) 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 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 Product (IP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Serious Adverse Events (SAEs) and 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) ≥ 3× upper limit of normal (ULN) **together with** TBL ≥ 2×ULN 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 ≥ 3 × ULN **together with** TBL ≥ 2 ×ULN, where no other reason, other than the IP, can be found to explain the combination of increases, e.g., 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 time frame 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 patient 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:

- Determine whether the patient 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 patient does not meet PHL criteria the Investigator will:

- 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 patient 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 patients who met PHL criteria prior to starting IP, 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 on an approach for the study patients' follow-up (including any further laboratory testing) and the continuous review of data.
- Subsequent to this contact the Investigator will:
  - Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
  - Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which the tests available in the Hy's Law lab kit should be used
  - Complete the 3 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 IP, 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 IP:

- 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:

- Provide 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 IP 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 met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review 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 patients 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 patients' 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 patient 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 (e.g., chronic or progressing malignant disease, severe infection or liver disease), or did the patient meet PHL criteria prior to starting study treatment and at first on-study treatment visit, as described in Section E 6 of this Appendix?

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 patient'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 patient'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

The list below represents the standard, comprehensive list of follow-up tests which are recommended but not mandatory and it may be modified based on clinical judgment. If required, additional assistance on which tests could be used to evaluate other potential causes of liver dysfunction consult with the Hepatic Safety Knowledge Group. Any test results need to be recorded.

Hy's Law lab kit for central laboratories

Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR
Viral hepatitis	Immunoglobulin M (IgM) anti-HAV IgM and Immunoglobulin G (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 is 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 GP, Watkins PB, Andrade RJ, Larrey D, Molokhia M, Takikawa H, et al 2011. Case definition and phenotype standardization in drug-induced liver injury. Clin Pharm Ther. 2011;89(6):806-15.

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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 Abreviations

Abbreviation	Explanation
$A_{2A}R$	Adenosine 2a receptor
ADA	Anti-drug antibody
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
BCRP	Breast cancer resistance protein
BP	Blood pressure
CD73	Cluster of differentiation 73: 5'-nucleotidase (5'-NT) or ecto-5'-nucleotidase
CI	Confidence interval
C_{max}	Maximum observed concentration
CNS	Central nervous system
CR	Complete response
CRP	C-reactive protein
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CCI	CCI
CYP	Cytochrome P450
DCO	Data cut-off
DILI	Drug induced liver injury
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EGFR	Epidermal growth factor receptor
EOT	End of treatment (visit)
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose positron emission tomography
FTIH	First-time-in-human
GCP	Good Clinical Practice

Abbreviation	Explanation
GGT	Gamma glutamyltransferase
HL	Hy's Law
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
IEC	Independent ethics committee
CCI	CCI
ILD	Interstitial lung disease
imAE	Immune-mediated adverse event
IP	Investigational product
IRB	Institutional Review Board
CCI	CCI
IV	Intravenous
IWRS	Interactive web response system
LDH	Lactate dehydrogenase
mAb	Monoclonal antibody
MATE1	Multidrug and toxin extrusion protein 1
mCRPC	Metastatic castration-resistant prostate carcinoma
MDSC	Myeloid-derived suppressor cells
MOA	Mechanism of action
MRI	Magnetic resonance imaging
MTD	Maximum-tolerated dose
MUGA	Multigated acquisition scan
NCI	National Cancer Institute
NE	Not evaluable
NHA	New hormonal agent(s)
NSCLC	Non-small cell lung cancer
NTL	Non-target lesion
OAT1	Organic anion transporter 1
OATP	Organic anion transporter polypeptide
OCT	Organic cation transporter
ORR	Overall response rate
CCI	CCI

Abbreviation	Explanation
PBMC	Peripheral blood mononuclear cells
PCWG3	Prostate Cancer Working Group 3
PD	Progression of disease
PD-1	Programmed cell death protein 1 (e.g., nivolumab [Opdivo®])
PD-L1	Programmed death ligand 1
CCI	CCI
PDx	Pharmacodynamics
PET	Positron emission tomography
PFS	Progression-free survival
P-gp	P-glycoprotein
PHL	Potential Hy's Law
PK	Pharmacokinetics
PO	*Per os* (orally)
PR	Partial response
PSA	Prostate-specific antigen
Q2W	Every 2 weeks
Q4W	Every 4 weeks
QD	Once daily
QRS	QRS complex; the main spike on an ECG line
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 Tumors
RP2D	Recommended Phase 2 dose
rPFS	Radiographic progression-free survival
SAE	Serious adverse event (see definition in Appendix B)
SD	Stable disease
SoA	Schedule of activities
SRC	Safety Review Committee
TBL	Total bilirubin
TBNK	Complete immune panel (T-, B-, and natural killer [NK] lymphocyte subsets)
TL	Target lesion
t_{max}	Time to reach C_{max}
TME	Tumor microenvironment
ULN	Upper limit of normal

Appendix G Guidelines for Evaluation of Objective Tumor Response Using RECIST Version 1.1 (Response Evaluation Criteria in Solid Tumors) in Soft Tissue and PCWG3 (Prostate Cancer Working Group Criteria 3) in Bone Lesions

INTRODUCTION

This appendix details the implementation of RECIST (Response Evaluation Criteria in Solid Tumors) 1.1 guidelines (Eisenhauer et al. 2009) and PCWG3 guidelines (Scher et al. 2016) for the D8731C00001 study with regards to Investigator assessment of tumor 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

Patients 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 subject, 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 tumor assessments for this study are highlighted, with the rationale provided.

Table 11 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 D8731C00001 study it is recommended that CT examinations of the chest, abdomen and pelvis will be used to assess tumor 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 D8731C00001 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 D8731C00001 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 tumor 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 D8731C00001 study, endoscopy and laparoscopy will not be used for tumor assessments as they are not validated in the context of tumor assessment.

CCI [redacted]

CCI [redacted]

CCI [redacted]

Cytology and histology

In the D8731C00001 study histology will not be used for tumor response assessments as per RECIST 1.1 and tumor response assessments will be performed on radiological criteria only.

FDG-PET scan

In the D8731C00001 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.

Tumor 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 subjects and should be performed no more than 28 days before allocation/randomization. The first follow-up assessment for Modules 1, 2, and 3 should be initially at 6 weeks (±1 week) following the start of AZD4635 dosing and subsequent assessments will be performed every 2 cycles (8 weeks, ±1 week) thereafter. 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 subject 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 subjects being assessed at a different frequency than other subjects.

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, embolization, 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 tumor visit response for TL.

Table 12 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

Table 12 Evaluation of target lesions

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

Non-Target lesions (NTL)

Evaluation of non-target lesions

All other lesions (or sites of disease), except for bone lesions, not recorded as TL should be identified as NTL at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits. At each visit an overall assessment of the NTL response should be recorded by the Investigator. This section provides the definitions of the criteria used to determine and record overall response for NTL at the investigational site at each visit.

Table 13 Evaluation of Non-Target Lesions

Complete Response (CR)	Disappearance of all non-target lesions since baseline. All lymph nodes must be non-pathological in size (< 10 mm short axis).
Non CR/Non PD	Persistence of one or more NTL
Progression (PD)	Unequivocal progression of existing non-target lesions. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.

Not Evaluable (NE)	Only relevant when one or some of the non-target lesions were not assessed and, in the Investigator's opinion, they are not able to provide an evaluable overall non-target lesion assessment at this visit. Note: For subjects without target lesions at baseline, this is relevant if any of the non-target lesions were not assessed at this visit and the progression criteria have not been met.

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

New Lesions

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

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

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

If a new lesion is equivocal, for example because of its small size, the treatment and tumor assessments should be continued until the new lesion has been confirmed. If repeat scans confirm there is a new lesion, then the progression date should be declared using the date of the initial scan.

Symptomatic deterioration

Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy.

Evaluation of Overall Visit Soft Tissue Response

The overall visit response will be derived using the algorithm shown in Table 14.

Table 14 Overall Visit Soft Tissue Response

Target lesions	Non-Target lesions	New Lesions	Overall soft tissue response
CR	CR	No	CR
CR	NA	No	CR

Table 14 Overall Visit Soft Tissue Response

Target lesions	Non-Target lesions	New Lesions	Overall soft tissue response
NA	CR	No	CR
CR	Non CR/Non PD	No	PR
CR	NE	No	PR
PR	Non PD or NE	No	PR
SD	Non PD or NE	No	SD
NA	Non CR/Non PD	No	SD (Non CR/Non PD)
NA	NA	No	NED
NE	Non PD or NE	No	NE
NA	NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable, NA = not applicable (only relevant if there were no TL and/or NTLs at baseline), NED = No Evidence of Disease (only relevant when there is no TL and NTL from baseline).

Specifications for radiological imaging

These notes are recommendations for use in clinical studies. The use of standardized protocols for CT and MRI allows comparability both within and between different studies, irrespective of where the examination has been undertaken.

CT scan

CT scans of the chest, abdomen, and pelvis should be contiguous throughout all the anatomical regions of interest.

The most critical CT image acquisition parameters for optimal tumor evaluation using RECIST Version 1.1 are anatomic coverage, contrast administration, slice thickness, and reconstruction interval.

Anatomic coverage

Optimal anatomic coverage for most solid tumors is the chest, abdomen and pelvis. Coverage 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 patients. Because a lesion later identified in a body part not scanned at baseline would be considered as a new lesion representing PD, careful consideration should be given to the extent of imaging coverage at baseline and at subsequent follow-up time

points. This will enable better consistency not only of tumor measurements but also identification of new disease.

Intravenous contrast administration

Optimal visualization and measurement of metastases in solid tumors requires consistent administration (dose and rate) of intravenous contrast as well as timing of scanning. Typically, most abdominal imaging is performed during the portal venous phase and (optimally) about the same time frame after injection on each examination. An adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient. It is very important that the same technique be used at baseline and on follow- up examinations for a given patient. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) should be performed should also be based on the tumor type and anatomic location of the disease and should be optimized to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of TLs on a different modality and interpretation of non-target disease or new lesions, since the same lesion may appear to have a different size using a new modality. Oral contrast is recommended to help visualise and differentiate structures in the abdomen.

If iodine contrast media is medically contraindicated at baseline or at any time during the course of the study then the recommended methods are CT thoracic examination without contrast and abdominal and pelvic MRI with contrast. If MRI cannot be performed, then a CT scan without IV contrast is an option for the thorax, abdomen, and pelvic examinations. For assessment of brain lesions, MRI is the preferred method.

Slice thickness and reconstruction material

It is recommended that CT scans be performed at 5 mm contiguous slice thickness and this guideline presumes a minimum 5 mm thickness in recommendations for the measurable lesion definition. Exceptionally, particular institutions may perform medically acceptable scans at slice thicknesses greater than 5 mm. If this occurs, the minimum size of measurable lesions at baseline should be twice the slice thickness of the baseline scans.

All window settings should be included in the assessment, particularly in the thorax where lung and soft tissue windows should be considered. When measuring lesions, the TLs should be measured on the same window setting for repeated examinations throughout the study. All images from each examination should be included in the assessment and not “selected” images of the apparent lesion.

MRI scan

MRI has excellent contrast, spatial and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity and measurement. Furthermore, the availability of MRI is variable globally. The modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. Generally, axial imaging of the abdomen and pelvis with T1 and T2 weighted imaging along with gadolinium-enhanced imaging should be performed. The field of view, matrix, number of excitations, phase encode steps, use of fat suppression and fast sequences should be optimized for the specific body part being imaged as well as the scanner utilized. It is beyond the scope of this appendix to prescribe specific MRI pulse sequence parameters for all scanners, body parts and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques if possible.

For these reasons, CT is the imaging modality of choice.

FDG-PET scans

FDG-PET has gained acceptance as a valuable tool for detecting, staging and restaging several malignancies. If FDG-PET scans are included in a protocol, an FDG uptake period of 60 minutes prior to imaging has been decided as the most appropriate for imaging of patients with malignancy. Whole-body acquisition is important since this allows for sampling of all areas of interest and assessment if new lesions have appeared thus determining the possibility of interval progression of disease. Images from the base of the skull to the level of the mid-thigh should be obtained 60 minutes post injection. PET camera specifications are variable and manufacturer specific, so every attempt should be made to use the same scanner, or the same model scanner, for serial scans on the same patient. Whole-body acquisitions can be performed in either 2- or 3-dimensional mode with attenuation correction, but the method chosen should be consistent across all patients and serial scans in the clinical study.

PET/CT scans

At present, low dose or attenuation correction CT portions of a combined PET/CT are of limited use in anatomically based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for tumor measurements by RECIST Version 1.1. In exceptional situations, if a site can document that the CT performed as part of a PET/CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the PET/CT can be used for RECIST measurements. However, this is not recommended because the PET portion of the CT introduces additional data that may bias an Investigator if it is not routinely or serially performed.

ASSESSMENT OF BONE LESION PROGRESSION USING PCWG3 CRITERIA

Bone lesions will be assessed by bone scan in addition to being part of the RECIST v1.1 malignant soft tissue assessment.

Method of assessment

Bone lesions identified on a whole body isotopic bone scan at baseline should be recorded and followed by the same method as per baseline assessment.

In the D8731C00001 study isotopic bone scans will be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. New lesions will be recorded where a positive and unequivocal hot-spot that was not present on the baseline bone scan assessment is identified on a bone scan performed at any time during the study. The Investigator should consider the positive hot-spot to be a significant new site of malignant disease and represent true disease progression in order to record the new lesion.

Tumor progression evaluation

Schedule of the evaluation

Baseline assessments should be performed no more than 28 days before the start of study treatment. The first follow-up assessment for Modules 1, 2, and 3 should be initially at 6 weeks (±1 week) following the start of AZD4635 dosing and subsequent assessments will be performed every 2 cycles (8 weeks, ±1 week) thereafter.

If an unscheduled assessment was performed and the subject 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 subjects being assessed at a different frequency than other subjects.

Documentation of lesions

All bone lesions (or sites of disease) should be identified by a bone scan at baseline. Their status should be followed at subsequent visits. At each visit an overall assessment of the bone lesion progression should be recorded by the Investigator. This section provides the definitions of the criteria used to determine and record bone progression at the investigational site at each visit.

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

- At the first bone scan post-baseline (6 weeks):

  2 or more new metastatic bone lesions are observed on the first 6-week scan compared to the baseline assessment. The confirmatory scan, performed at least 6 weeks later and preferably no later than the next scheduled visit for a bone scan (i.e., Week 12), must show 2 or more additional new metastatic bone lesions (for a total of 4 or more new metastatic bone lesions since the baseline assessment) for progression to be documented.

Note - The first bone scan completed after baseline will be considered the '6-week scan' regardless if taken at week 6 or at an unscheduled assessment.

- After the first bone scan post-baseline (6 weeks):
  2 or more new metastatic bone lesions are observed compared to the 6‑week assessment. The confirmatory scan, performed at least 6 weeks later and preferably at the next scheduled visit for a bone scan, must show the persistence of or an increase in the number of metastatic bone lesions compared to the prior scan for progression to be documented.

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

Evaluation of bone progression status

Table 15 provides the definitions for the visit bone progression status for bone lesions.

Table 15 Bone progression status

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

OVERALL RADIOLOGICAL VISIT ASSESSMENT

Table 16 provides the definitions how the visit responses for soft tissue (according to RECIST1.1 criteria) and bone progression status (according to PCWG3 criteria) are combined to give an overall radiological objective visit response.

Table 16 Overall radiological visit response

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

Table 16 Overall radiological visit response

Overall visit soft tissue response (RECIST 1.1)	Bone progression status (PCWG3)	Bone lesions at visit Present/Absent	Overall radiological visit response
PD	Any	Any	PD
Any	PD	Any	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable, NED = No Evidence of Disease (only relevant when there is no TL and NTL from baseline).

CONFIRMATION OF RESPONSE

In the D8731C00001 study, imaging for confirmation of response (CR or PR) should be performed at the next scheduled RECIST and PCWG3 assessment, i.e., 8 weeks (and must not be less than 4 weeks later) following the date the criteria for response were first met.

Table 17 Best overall response when confirmation of CR and PR required.

Overall radiological response First time point	Overall radiological response subsequent time point	Best Overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD or PD
CR	PD	SD or PD
CR	NE	SD or NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD or PD
PR	NE	SD or NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable.

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

Appendix H CCI

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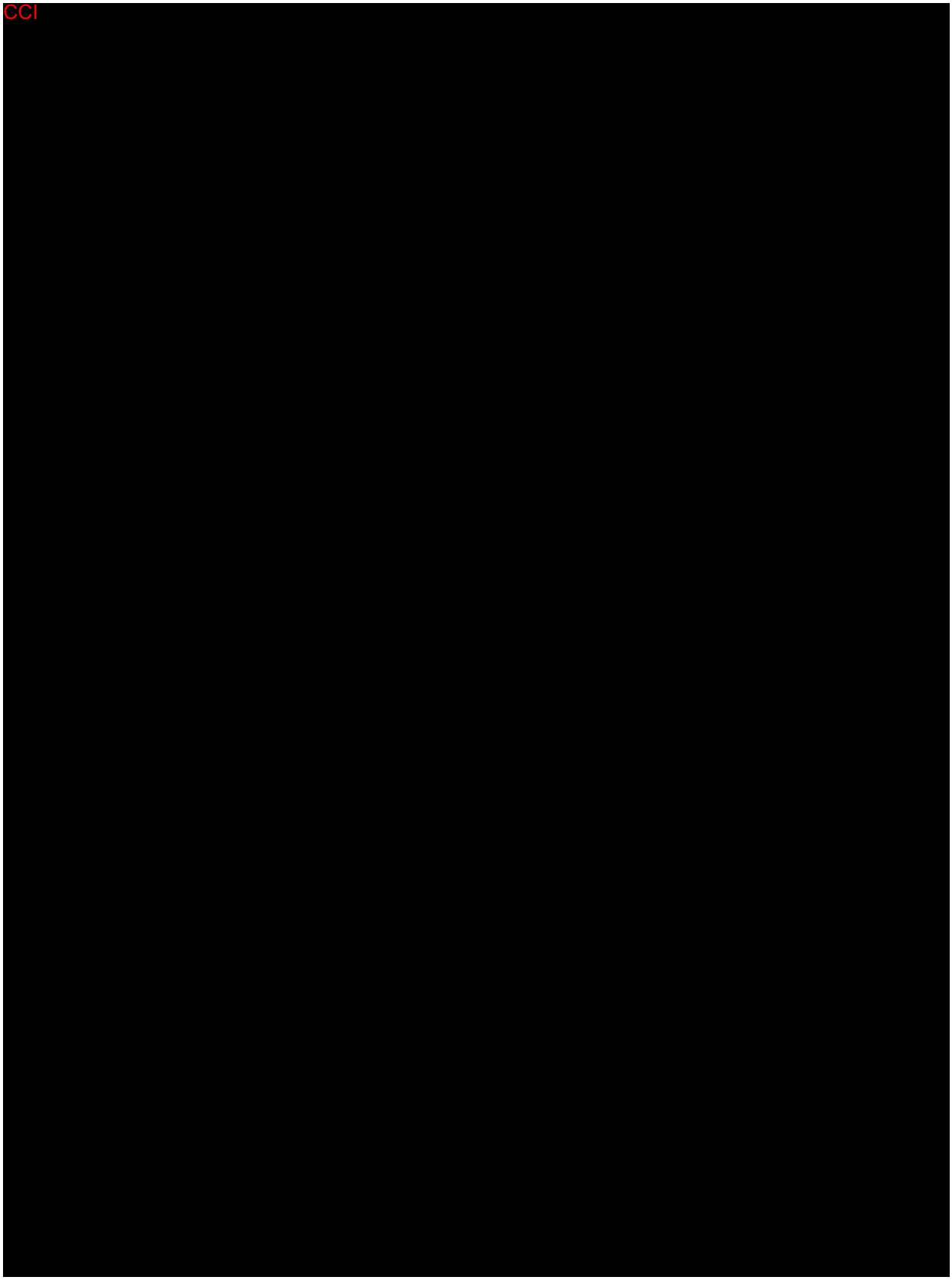

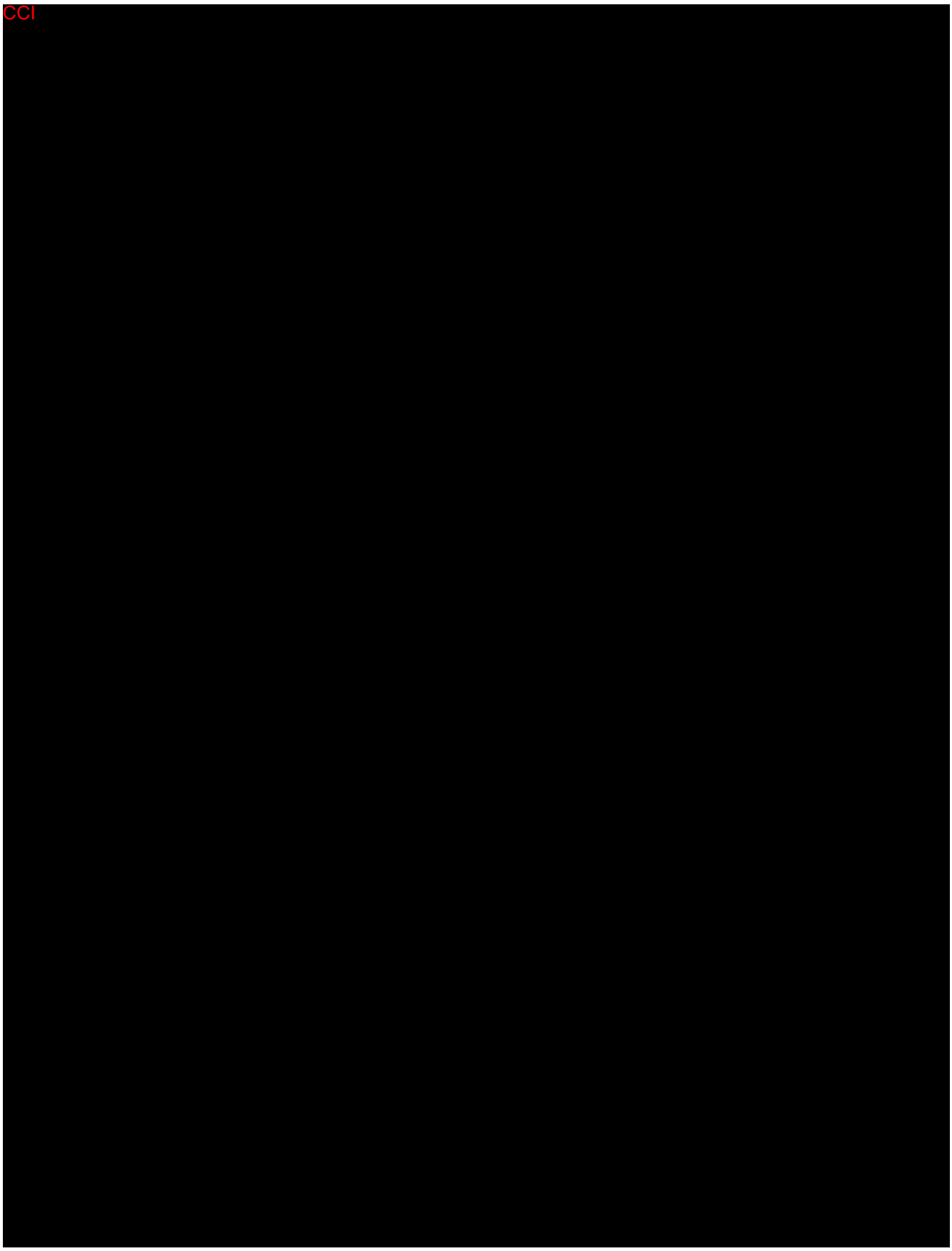
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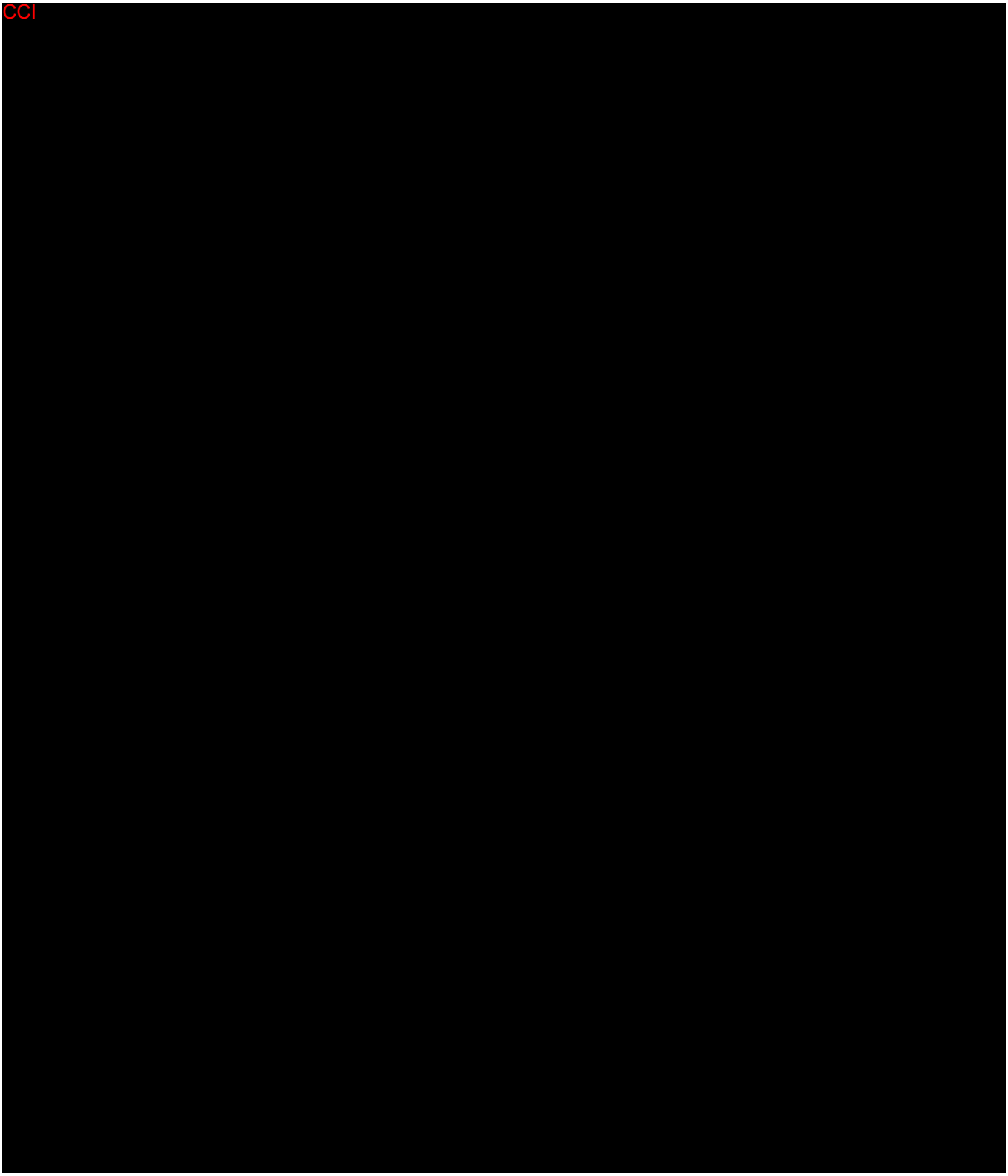
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Appendix I PCWG3 PSA Criteria

Baseline/Study Entry

PSA progression requirements for study entry

Patients 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 pure small cell carcinoma). It is recommended to estimate a pretreatment PSA doubling time (PSADT) if at least 3 values are available ≥4 weeks apart. Treatment or enrollment onto a trial should not be delayed to estimate PSADT.

On-Study Disease Assessments

- PSA results are to be collected on Day 1 of each treatment cycle
  - Continue through early rises for a minimum of 12 weeks unless there is other evidence of progression, as a favorable effects on PSA may be delayed for ≥12 weeks
  - Ignore PSA rises before 12 weeks in determining PSA response

Patients with PSA progression are allowed and encouraged to continue treatment until symptomatic or radiographic progression.

Reference: Scher et al. 2016

Appendix J Disallowed medications

Contribution of CYP1A2 to AZD4635 metabolism appears to be >80%. The following CYP1A2 strong and moderate inducers and inhibitors (Table 19) 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 19 Examples of CYP1A2 inhibitors and inducers of

CYP1A2	Strong inhibitors	Moderate inhibitors
	Ciprofloxacin, clinafloxacin, enoxacin, fluvoxamine[a], 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

[a] Strong inhibitor of CYP1A2 and CYP2C19, and moderate inhibitor of CYP2D6 and CYP3A.

Use of inhibitors or inducers of BCRP and sensitive substrates of OATP1B1/3, OAT1, OCT1, OCT2, MATE1 and P-gp is not permitted from 2 weeks before the first dose of AZD4635 until at least 2 weeks after the last dose of AZD4635.

Examples of sensitive substrates of these substrates aboveare presented in Table 20.

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. If medically feasible, patients taking regular medication, with the exception of examples of known substrates of transporters listed in Table 20, should be maintained on it throughout the study period.

Table 20 Examples of substrates of transporters

Substrate category	Examples of drugs in the category
Sensitive substrates of:	
BCRP	Methotrexate, mitoxantrone, imatinib, lapatinib, sulfasalazine, topotecan, daunorubicin, doxorubicin, SN-38, irinotecan, prazosin, pantoprazole, atorvastatin, fluvastatin, rosuvastatin, simvastatin.

Substrate category	Examples of drugs in the category
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

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