Parexel International

AstraZeneca

D601HC00002

A Phase 2b, Open-label, Single-arm, Multi-centre Study assessing the Efficacy and Safety of Adavosertib as Treatment for Recurrent or Persistent Uterine Serous Carcinoma (ADAGIO)

Statistical Analysis Plan

Version: 2.0

Parexel Project Number: 247600

TABLE OF CONTENTS

REVISION HISTORY

Version No.	Effective Date	Summary of Change(s)
1.0	[9 Oct 2020]	New document
1.1	[22 Jan 2021]	1. Section 4.1 Added a paragraph related to participants who failed screening and later rescreened. 2. CCAS was removed from Table 1 under CCI section as per AZ study team request.
1.2	[15 Mar 2021]	Added a footnote to Table 3 in section 3.1.1.
1.3	[22 Apr 2021]	Additional safety haematology and clinical chemistry assessment been added in section 173.1.1 Table 3 and Schedule of Assessments in Appendix A following Protocol update.
1.4	[13 Jul 2021]	The imputation rule of AE date updated in section 4.1.1 as per AZ comments from IDMC1 delivery.
1.5	[10 Sep 2021]	"Please note radiotherapy is not considered as subsequent cancer therapy while calculating ORR." was added to section 3.3.1 as per AZ study team suggestion. Sensitivity analyses will be performed based on BICR assessments instead of investigator data as per AZ team request.
2.0	[17 June 2022]	In Section 1.1 All exploratory objectives will not be included in CSR. In Section 1.3 Final analysis DCO is removed and in Sections 3.1, 3.2.4 and 4.2.6 reference to final analysis was replaced by primary analysis. In Section 2.2, CrCl >50 mL/min is added under inclusion criteria 9. Inclusion criteria 1, exclusion criteria 9 and 14 are added. In Section 3.1 End of study definition has changed. In section 3.2, the sentence on sensitivity analysis is deleted as it will not be presented in CSR. In Section 3.3.3 Duration of response will be presented in months is added.

		In Section 4.2.1.1 'and participants who did not receive' treatment is deleted from the first bullet as the team agreed to consider this category as screen failure. In Section 4.2.2.2 reference to the duration of response outputs for patients with 6 months follow-up is removed.

LIST OF ABBREVIATIONS

Abbreviation / Acronym	Definition / Expansion
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	anatomical therapeutic chemical
BICR	Blinded Independent Central Review
BLQ	below the lower limit of quantitation
BMI	body mass index
BoR	Best Objective Response
CCI [redacted]	
CCAS	centrally confirmed analysis set
CI	confidence interval
C_{max}	maximum concentration
CR	complete response
CRF	case report form
CSP	clinical study protocol
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CCI [redacted]	
C_{trough}	concentration trough
CV	coefficient of variation
d.p	decimal place
DBL	Database lock
DBP	diastolic blood pressure
DCO	data cut-off
DCR	disease control rate
DMC	data monitoring committee
CCI [redacted]	
DoR	duration of response

Abbreviation / Acronym	Definition / Expansion
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
CCI [redacted]	
FAS	full analysis set
FIGO	International Federation of Gynecology and Obstetrics
FFPE	formalin-fixed paraffin-embedded
Hb	Haemoglobin
HER2	human epidermal growth factor receptor 2
CCI [redacted]	
ICF	informed consent form
CCI [redacted]	
INR	International Normalised Ratio
IPD	important protocol deviation
LD	longest diameter
LPFD	last participant first dose
LPLV	last participant last visit
MRI	magnetic resonance imaging
NA	not applicable
NE	not evaluable
CCI [redacted]	
NQ	not quantifiable
NTL	non-target lesion
ORR	objective response rate
OS	Overall survival
PD	progressive disease
PFS	Progression-free survival
PFS6	Progression-free survival at 6 months
CCI [redacted]	

Abbreviation / Acronym	Definition / Expansion
CCI	
PK	Pharmacokinetic
PR	partial response
CCI	
PT	preferred term
QD	once daily
RDI	relative dose intensity
RECIST v1.1	Response Evaluation Criteria in Solid Tumors
CCI	
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	stable disease
SoA	schedule of assessments
SOC	system organ class
StD	Standard Deviation
TEAE	treatment-emergent adverse event
TL	target lesion
USC	uterine serous carcinoma
VEGF	vascular endothelial growth factor
WHO	World Health Organization

1 STUDY DETAILS

The analyses described in this statistical analysis plan (SAP) are based upon the following study documents:

- Clinical Study Protocol, Version 6.0 (20th May 2022)

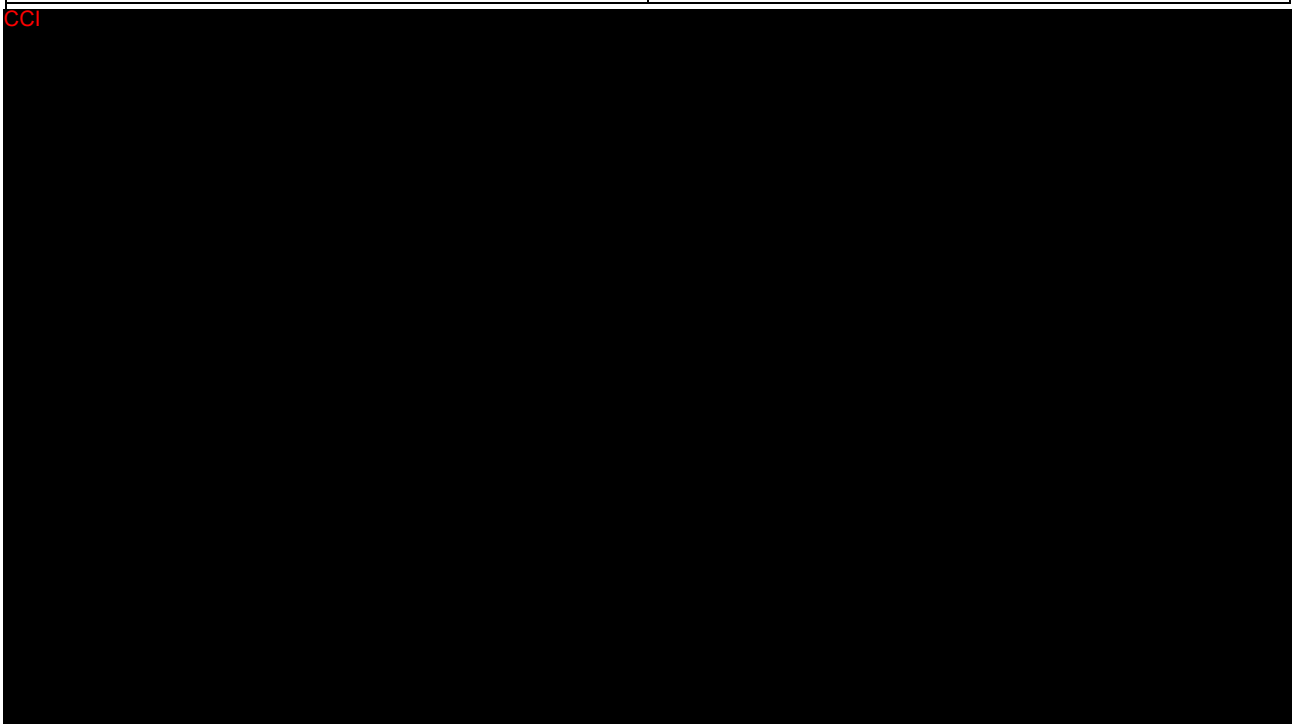
1.1 Study Objectives

The exploratory objectives (in grey) are not part of the CSR and will not be analysed by Parexel.

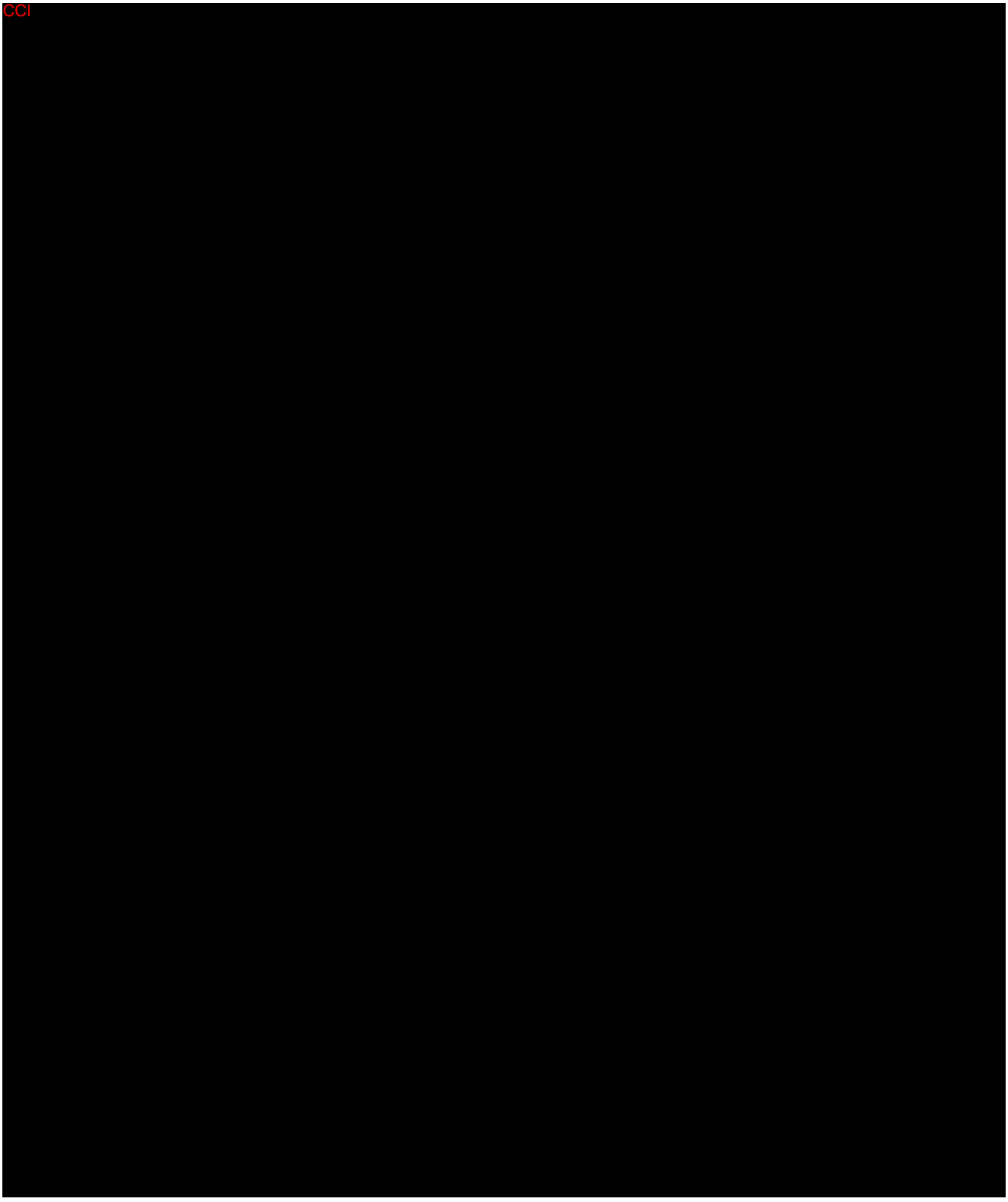
Objectives	Endpoints/Variables
Primary	
To evaluate the efficacy of adavosertib by the assessment of objective response rate (ORR).	ORR is defined as the proportion of participants with measurable disease at baseline who have a confirmed complete response (CR) or partial response (PR), as determined by Blinded Independent Central Review (BICR) per RECIST v1.1.
Secondary	
To evaluate the efficacy of adavosertib by assessment of duration of response (DoR).	DoR is defined as the time from the date of first documented response until date of documented progression per RECIST v1.1 as assessed by Blinded Independent Central Review (BICR), or death in the absence of disease progression.
To evaluate the efficacy of adavosertib by assessment of the depth of response.	Depth of response is defined as the best percentage change from baseline in Target Lesions.
To evaluate the efficacy of adavosertib by assessment of progression-free survival (PFS).	PFS is defined as time from date of first dose until progression per RECIST v1.1 as assessed by BICR, or death due to any cause.
To evaluate the efficacy of adavosertib by assessment of PFS6.	PFS6 is defined as the proportion of participants alive and progression free at 6 months and will be reported as the Kaplan-Meier estimate of PFS per RECIST v1.1 as assessed by BICR at 6 months.
To evaluate the efficacy of adavosertib by assessment of overall survival (OS).	OS is defined as time from date of first dose until the date of death due to any cause.

To evaluate the efficacy of adavosertib by assessment of disease control rate (DCR).	DCR is defined as the percentage of participants who have a best overall response of CR or PR or who have stable disease for at least 5 weeks after start of treatment (to allow for an early assessment within the assessment window).
To evaluate the pharmacokinetics of adavosertib.	Plasma concentration of adavosertib: C_{trough} (pre-dose) and C_{max}.
To assess the safety and tolerability of adavosertib in participants with USC.	Safety and tolerability will be evaluated in terms of adverse events (AEs), vital signs, clinical laboratory assessments, ECGs, and AEs leading to dose interruptions, dose reductions, and dose discontinuations. Vital signs parameters include systolic and diastolic blood pressure, and pulse as well as heart rate, body temperature, body weight, height and body mass index (BMI). Laboratory parameters include clinical chemistry and haematology parameters as well as urinalysis.

CCI



CCI



.

RECIST v1.1, Response Evaluation Criteria in Solid Tumors. AE, adverse event; BICR, Blinded Independent Central Review; BMI, body mass index; C_{max}, maximum concentration; C_{trough}, lowest concentration; CR, complete response; CTCAE v5.0, Common Terminology Criteria for Adverse Events Version 5.0; CCI DCR,

disease control rate; CCI DoR, duration of response; ECG, electrocardiogram; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PFS6, proportion of participants alive and progression free at 6 months; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors; CCI SAE, serious adverse event; USC, uterine serous carcinoma. CCI ORR, objective response rate; PFS6, proportion of participants alive and progression free at 6 months; CCI PK, Pharmacokinetics.

1.2 Study Design

This is a Phase 2b, single-arm, open-label, multi-centre study to assess the efficacy and safety of adavosertib in eligible participants with histologically confirmed recurrent or persistent USC for the purposes of this study, this includes participants with endometrial carcinoma of mixed histology where the serous component comprises at least 10% of the tumour [1]), evidence of measurable disease as per RECIST v1.1, and who have received at least 1 prior platinum-based chemotherapy regimen for the management of USC. Participants with carcinosarcomas are not eligible.

Approximately 120 eligible participants will receive oral adavosertib 300 mg once daily (QD) for 5 days followed by 2 days off in Weeks 1 and 2 out of a 21-day cycle until objective radiological disease progression by investigator assessment using RECIST v1.1, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

For the Schedule of Assessments (SoA), see Appendix A. The study design schema (Figure 1) and study flow chart (Figure 2) can be found in Appendix B.

1.3 Timing of Analysis

The primary analysis will be performed in both locally and centrally confirmed USC populations, 6 months after the last participant first dose, or when all participants have progressed or died due to any cause, whichever is earlier. Maturity of DoR data will also be taken into account when selecting the DCO date for primary analysis. An interim analysis is planned after approximately 30 participants in the Centrally Confirmed Analysis Set (CCAS) have had the opportunity to be treated for at least 4 months. Recruitment will not be paused whilst the participants required for the interim analysis are evaluated.

1.4 Number of Participants

Approximately 120 participants will be enrolled and dosed, with an intent to include approximately 40 participants or more who have previously been exposed to PD-1/PD-L1 inhibitors. The primary objective is to estimate ORR and no formal statistical comparisons will be performed. With 120 participants, if the observed ORR is CCI the width of the 2-sided 90% CI will be CCI

2 ANALYSIS SET

2.1 Definition of Analysis Sets

The primary analysis population is the FAS. In addition, the CCAS population is the key subgroup for decision making. Details of the analysis sets are presented in Table 1 and Table 2.

Table 1 Analysis Sets

Population/Analysis Set	Description
All Participants	The All Participants Set will include all participants who have signed the informed consent form (ie, screening failures plus participants dosed). The All Participants Set will be used to describe participant disposition.
Full Analysis Set (FAS)	The Full Analysis Set (FAS) will include all participants who received at least one (non-zero) dose of study treatment. This population will be used for the primary analyses of the efficacy and safety endpoints.
Centrally Confirmed Analysis Set (CCAS)	The Centrally Confirmed Analysis Set (CCAS) will include all centrally-confirmed USC participants who received at least one (non-zero) dose of study treatment. This population will be used for the analyses of efficacy.
Pharmacokinetic Analysis Set	The pharmacokinetic (PK) analysis set will include all dosed participants who had at least one measurable plasma concentration collected post-dose which was obtained without any deviation or event thought to significantly affect the PK analysis. All plasma concentration data will be summarized and presented according to AstraZeneca standards. This population will be used for the analysis of the PK data.

Table 2 Summary of outcome variables and analysis sets

Outcome variable	Analysis Sets
Participant disposition	All Participants
Demography and baseline characteristics	Full analysis set
Safety data	
Exposure	Full analysis set
Adverse Events	Full analysis set
Laboratory measurements	Full analysis set
Vital Signs/ECG/Physical examination	Full analysis set
Concomitant medications	Full analysis set
Efficacy Data	
Objective Response Rate	Full analysis set, CCAS
Duration of Response	Full analysis set, CCAS
Depth of Response	Full analysis set, CCAS
PFS	Full analysis set, CCAS
PFS6	Full analysis set, CCAS
OS	Full analysis set, CCAS
DCR	Full analysis set, CCAS
CCI [redacted]	Full analysis set
Pharmacokinetics	
Plasma Pharmacokinetic variables	PK analysis set

2.2 Protocol Deviations

Important protocol deviations (IPDs) are defined as those deviations from the protocol likely to have an impact on the perceived efficacy and/or safety of study treatments. The impact of important protocol deviations on the efficacy and/or safety results will be investigated by assessing the robustness of the study results and conclusions to the choice of analysis set, both including and excluding data potentially affected by important protocol deviations.

Important protocol deviations and any action to be taken regarding the exclusion of participants or affected data from specific analyses are defined in the project-specific Protocol Deviation Specification.

For this study, the following general categories will be considered IPDs and will be summarized in the Clinical Study Report (CSR):

- Deviation 1: Participants who received treatment and who deviated from the following key entry criteria in the Clinical Study Protocol (CSP):

- Inclusion criteria 1: Capable of giving signed informed consent and has given signed informed consent as described in Appendix C of CSP which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.
- Inclusion Criteria 4: Histologically confirmed recurrent or persistent USC. For the purposes of this study, participants with endometrial carcinoma of mixed histology where the serous component comprises at least 10% of the tumour will be considered eligible. Participants with carcinosarcomas are not eligible.
- Inclusion Criteria 5: Evidence of measurable disease as per RECIST v1.1 defined as at least one lesion, not previously irradiated, that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥10mm with computed tomography (CT) scan or magnetic resonance imaging (MRI) (except lymph nodes which must have short axis ≥15mm) and which is suitable for accurate repeated measurements.
- Inclusion Criteria 6: At least 1 prior platinum-based chemotherapy regimen for the management of USC (there is no restriction on the number of prior lines of systemic therapy that a participant may have previously received, and the platinum-based chemotherapy may have been given in the adjuvant setting). Chemotherapy administered only in conjunction with primary radiotherapy as a radiosensitiser should not count as a systemic regimen.
  - Prior anticancer therapies (eg, immune checkpoint inhibitors, vascular endothelial growth factor (VEGF) inhibitors and HER2 targeted therapy) are allowed.
- Inclusion Criteria 7: Eastern Cooperative Oncology Group (ECOG) performance status 0-1
- Inclusion Criteria 9: Participants must have normal organ and marrow function at baseline, as defined below by laboratory values within 7 days prior to study drug(s) administration:
  - Absolute neutrophil count (ANC) ≥1.5 × 109/L
  - Haemoglobin (Hb) ≥ 9 g/dL
  - Platelet count ≥ 100 × 109/L

    Calculated creatinine clearance (CrCl) >50 mL/min as determined by the Cockcroft-Gault method (using actual body weight).
- Exclusion criteria 9: History of Torsades de pointes unless all risk factors that contributed to Torsades have been corrected.
- Inclusion Criteria 10: Consent to submit and provide a mandatory FFPE tumour sample for central testing. The site must confirm that the FFPE sample is available prior to dosing.
- Exclusion Criteria 13: Use of anticancer treatment drug ≤ 21 days (≤ 6 weeks for nitrosoureas or mitomycin C) or use of an investigational product within 5 half-lives prior to the first dose of adavosertib. For PD-1/PD-L1 inhibitors, a minimum of 28 days since last dose is required.

  Patients on luteinising-hormone releasing hormone analogue treatment for more than 6 months are allowed entry into the study and may continue at the discretion of the investigator.

  - Exclusion criteria 14: Palliative radiotherapy with a limited field of radiation within 2 weeks or with wide field of radiation or to more than 30% of bone marrow within 4 weeks prior to the first dose of study intervention.
  - Exclusion Criteria 16: Prior receipt of a cell cycle checkpoint inhibitor (eg, CHK1, WEE1, or ATR inhibition)
- Deviation 2: Patients assigned to treatment who received their assigned study treatment at an incorrect dose at more than 1 occasion.
- Deviation 3: Persistently missing important protocol required safety assessments (haematology, liver function test, chemistry panel and/or as per medical monitor discretion) and potentially having major impact to patient safety (clinical review on a case by case base).
- Deviation 4: Baseline RECIST >42 days before start of assigned treatment (unless agreed with medical team), or no baseline RECIST 1.1 assessment on or before start of treatment.
- Deviation 5: Patient received study treatment, but post-baseline tumour assessment scans not performed at all or major issues with scans not being performed in accordance with the protocol.
- Deviation 6: Prohibited or restricted concomitant medications or therapies have been used.
- Deviation 7: Met study treatment discontinuation criteria but continued study treatment and potentially had major impact to patients' safety according to clinical judgement.
- Deviation 8: Patient met criteria for RECIST v1.1-defined radiological progression, but was not withdrawn from study treatment.
- Deviation 9: Missed visits, assessments, or treatments that, in the opinion of the principal investigator, were due to the COVID-19 global pandemic and there was a significant effect on EITHER completeness, accuracy, and/or reliability of the participant's data, OR the participant's rights, safety or well-being.
- Deviation 10: Dose was re-escalated for subject.
- Deviation 11: Participant received another systemic anti-cancer therapy during study conduct, but did not discontinue the study treatment.

Deviations not pre-specified in the above list that are considered to be important by the study team will also be classified as IPD's.

The number and percentage of participants with any IPD will be summarized for each IPD category based on the FAS. Participants with more than one deviation in the same IPD category will be counted once for that IPD category. Any participants who have deviations in more than one IPD category will be counted once in the overall summary.

A list of all protocol deviations, including those reported by monitors, will be reviewed and decisions regarding how to handle these deviations will be documented by the study team physician, clinical pharmacology scientist and statistician prior to database lock. The final classification will be made prior to database lock.

A by-participant listing of important protocol deviations will be provided.

3 PRIMARY AND SECONDARY VARIABLES

3.1 General Principles

Baseline measurements and change from baseline variables

Baseline will be the last non-missing value obtained prior to the first dose/administration of study medication and any information taken after first dose/administration of study medication will be regarded as post baseline information. If two visits are equally eligible to assess participant status at baseline (e.g., screening and baseline assessments both on the same date prior to first dose/administration), the average should be taken as the baseline value. For non-numeric laboratory tests (i.e., some of the urinalysis parameters) where taking an average is not possible, then the clinical favourite value would be taken as baseline (i.e., normal and abnormal were observed on the same date prior to first dose/administration, then normal is considered as baseline value). In the scenario where there are two assessments on Day 1 prior to the first dose, one with time recorded and the other without time recorded, the one with time recorded would be selected as baseline. For assessments on the day of first dose where time is not captured, a nominal pre-dose indicator, if available, will serve as sufficient evidence that the assessment occurred prior to first dose. Where safety data are summarised over time, study day will be calculated in relation to date of first treatment. If no value exists before the first dose/administration, then the baseline value will be treated as missing.

In all summaries, change from baseline variables will be calculated as the post treatment value minus the value at baseline. For % change from baseline, calculate:

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

Study Day 1 is defined as the date of first dose of study treatment. For visits (or events) that occur on or after first dose, study day is defined as

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

For visits (or events) that occur prior to first dose, study day is defined as

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

There is no Study Day 0.

End of Study Definition

A participant is considered to have completed the study if she has completed all phases of the study including the last scheduled procedure shown in the Schedule of Activities (SoA) Appendix A. The end of the study is defined as the date of the last visit of the last participant in the study. The last visit occurs when the last participant has their last scheduled visit, or 6 months after last participant first dose, whichever comes first.

After the primary analysis data cut-off (DCO), the clinical study database will be closed to new data. The primary analysis DCO will be followed by clinical database lock when all data for all participants have been collected.

The study may be terminated at individual centres if the study procedures are not being performed according to Good Clinical Practice (GCP), or if recruitment is slow. AstraZeneca may also terminate

the entire study prematurely if concerns for safety arise within this study or in any other study with adavosertib.

Participants will continue to be monitored by their treating physician/investigator for all SAEs and pregnancies while receiving IPs and for 30 days after the last dose of IP.

3.1.1 Definitions of Visit Windows

Analysis visit windows are displayed in SoA (Appendix A) for all assessments. Vital signs, ECG, laboratory and PK data are all cycle-based will be mapped as shown in Table 3. [redacted]

Table 3 Visit Windowing for laboratory assessments, vital signs, ECG and PK

Visit window label	Visit window
Screening	[28 days prior to first dose; 1 day prior to first dose]
C1 D1	Day of first dose in Cycle 1 (exact)
C1 D5	[Day 4 in Cycle 1, Day 5 in Cycle 1]*
	[Day 4 in Cycle 1, Day 6 in Cycle 1]
C1 D8	[Day 8 in Cycle 1, Day 10 in Cycle 1]
C1 D15	[Day 14 in Cycle 1, Day 16 in Cycle 1]
C2 D1	Day of first dose in Cycle 2 (exact)
C2 D5	[Day 4 in Cycle 2, Day 5 in Cycle 2]*
	[Day 4 in Cycle 2, Day 6 in Cycle 2]
C2 D8	[Day 8 in Cycle 2, Day 10 in Cycle 2]
C2 D15	[Day 14 in Cycle 2, Day 16 in Cycle 2]
C3 D1	[Day 1 in Cycle 3, Day 4 in Cycle 3]
C3 D8	[Day 8 in Cycle 3, Day 10 in Cycle 3]
etc…**	etc…

*Visit windowing is only for PK assessment.

**Cycle 4 and all subsequent visits will be similar to cycle 3.

The following conventions should apply:

- The analysis visit window should be exhaustive so that data recorded at any time point has the potential to be summarized. Inclusion within the analysis visit window should be based on the actual date and not the intended date of the visit.
- All unscheduled visit data will have the potential to be included in the summaries.
- Visits post treatment discontinuation will not be assigned to visit windows but presented as scheduled.
- For summaries showing the maximum or minimum values, the maximum/minimum value recorded on treatment will be used (regardless of where it falls in an interval).
- Listings should display all values contributing to a time point for a participant.
- For visit based summaries, if there is more than one value per participant within a time window then the closest value to the scheduled visit date should be used, or the earlier in the event the values are equidistant from the nominal visit date. If there are two values recorded on the same day and the parameter is CTCAE gradable then the record with the highest toxicity grade should be used.
- Note: in summaries of extreme values all post baseline values collected are used including those collected at unscheduled visits regardless of whether or not the value is closest to the scheduled visit date.
- For summaries at a participant level, all values should be included, regardless of whether they appear in a corresponding visit-based summary, when deriving a participant level statistic such as a maximum.

3.1.1.1 Visit Windows for Tumour Assessments

The following conventions will apply for tumour assessment data:

- All tumour assessments available during the study should be used for the efficacy analysis. A windowing rule will be applied and will follow the CSP allowed visit window; therefore, any RECIST assessment performed within ± 7 days of the CSP scheduled visit will be used for that visit.
- If there are any assessments outside these visit windows, they will also be included in the closest visit window following the intent-to-treat principle. The tumour assessments which

are outside the visit windows will be flagged in the data listings.

The above could result in more than one tumour assessments within a window and in that case, the one closest to the scheduled assessment will be used.

3.2 Derivation of RECIST Visit Responses

For all participants, the RECIST tumour response data will be used to determine each participant's visit response according to RECIST version 1.1. It will also be used to determine if and when a participant has progressed in accordance with RECIST and their objective response to study treatment.

Baseline radiological tumour assessments are to be performed no more than 28 days before the start of randomised treatment and ideally as close as possible to the start of study treatment. Tumour assessments are then performed every 6 weeks (±7 days) following the start of study treatment for the first 48 weeks then every 9 weeks (±7 days) thereafter, until objective radiological disease progression by investigator assessment using RECIST v1.1.

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

For ORR, a visit response of CR or PR must be confirmed by a subsequent scan conducted at least 4 weeks after the initial response is observed. The next RECIST scheduled assessment can be used for the confirmatory scan.

The RECIST tumour response data will be used to determine each participant's visit response according to RECIST version 1.1. At each visit, participants will be programmatically assigned a RECIST 1.1 visit response of CR, PR, SD, PD or NE, using the information from target lesions (TLs), non-target lesions (NTLs) and new lesions and depending on the status of their disease compared with baseline and previous assessments. If a participant has had a tumour assessment that cannot be evaluated then the participant will be assigned a visit response of not evaluable (NE), (unless there is evidence of progression in which case the response will be assigned as PD).

Please refer to Section 3.2.1 for the definitions of CR, PR, SD, PD and NE.

RECIST outcomes (i.e. confirmed ORR, DoR, percentage change from baseline in tumour size, PFS, and DCR.) will be calculated programmatically from the RECIST tumour response data.

RECIST outcomes will be derived using RECIST v1.1 assessments based on BICR (see Section 3.2.4). The efficacy analysis will be based on BICR assessments.

3.2.1 Target lesions (TLs) – site investigator data

Measurable disease is defined as having at least one measurable lesion, not previously irradiated, which is ≥ 10 mm in the longest diameter (LD), (except lymph nodes which must have short axis ≥ 15 mm) with CT or MRI and which is suitable for accurate repeated measurements. A participant can have a maximum of five measurable lesions recorded at baseline with a maximum of two lesions per organ (representative of all lesions involved and suitable for accurate repeated measurement) and

these are referred to as target lesions (TLs). If more than one baseline scan is recorded then measurements from the one that is closest and prior to first dose/administration of study medication will be used to define the baseline sum of TLs. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

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

Note: For participants who do not have measurable disease at entry (i.e. no TLs) but have non-measurable disease, evaluation of overall visit responses will be based on the overall NTL assessment and the absence/presence of new lesions (see Section 3.2.2 for further details). If a participant does not have measurable disease at baseline then the TL visit response will be not applicable (NA). This will be a protocol deviation for this study.

Table 5 TL Visit Responses (RECIST 1.1)

Visit Responses	Description
Complete response (CR)	Disappearance of all TLs since baseline. Any pathological lymph nodes selected as TLs must have a reduction in short axis diameter to <10 mm.
Partial response (PR)	At least a 30% decrease in the sum of the diameters of TL, taking as reference the baseline sum of diameters
Progressive disease (PD)	At least a 20% increase in the sum of diameters of TLs, taking as reference the smallest previous sum of diameters (nadir) – 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 from nadir
Stable disease (SD)	Neither sufficient decrease in sum of diameters to qualify for PR nor sufficient increase to qualify for PD
Not evaluable (NE)	Only relevant if any of the TLs at follow-up were not assessed or not evaluable (eg, missing anatomy) 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 TL response
Not applicable (NA)	Only relevant if no TLs present at baseline

Rounding of TL data

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

Missing TL data

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

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

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

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

If all TL measurements are missing, then the TL visit response is NE. Overall visit response will also be NE, unless there is a progression of non-TLs or new lesions, in which case the response will be PD.

Lymph nodes

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

TL visit responses subsequent to CR

Only CR, PD or NE can follow a CR. If a CR has occurred, then the following rules at the subsequent visits must be applied:

- Step 1: If all lesions meet the CR criteria (i.e. 0mm or < 10mm for lymph nodes) then response will be set to CR irrespective of whether the criteria for PD of TL is also met i.e. if a lymph node short axis increases by 20% but remains < 10mm.
- Step 2: If some lesion measurements are missing but all other lesions meet the CR criteria (i.e. 0mm or < 10mm for lymph nodes) then response will be set to NE irrespective of whether, when referencing the sum of TL diameters, the criteria for PD are also met.
- Step 3: If not all lesions meet the CR criteria (i.e. a pathological lymph node selected as TL has short axis > 10mm or the reappearance of previously disappeared lesion) or a new lesion appears, then response will be set to PD
- Step 4: If after steps 1 – 3 a response can still not be determined the response will be set to remain as CR

TL too big to measure

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

TL too small to measure

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

Irradiated lesions/lesion intervention

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

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

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

- Step 2: If there was no evidence of progression after step 1, treat the lesion diameter (for those lesions with intervention) as missing and if ≤ 1/3 of the TLs have missing measurements then scale up as described in the 'Scaling' section below. If the scaling results in a visit response of PD then the participant would be assigned a TL response of PD.

- Step 3: If, after both steps, PD has not been assigned, then, if appropriate (i.e. if ≤ 1/3 of the TLs have missing measurements), the scaled sum of diameters calculated in step 2 should be used, and PR or SD then assigned as the visit response. Participants with intervention are evaluable for CR as long as all non-intervened lesions are 0 (or <10mm for lymph nodes) and the lesions that have been subject to intervention also have a value of 0 (or <10mm for lymph nodes) recorded. If scaling up is not appropriate due to too few non-missing measurements, then the visit response will be set as NE.

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

Scaling (applicable only for irradiated lesions/lesion intervention)

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

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

Example of scaling

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

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

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

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

68 x 74 / 62 = 81 mm

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

Lesions that split in two

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

Lesions that merge

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

Change in method of assessment of TLs

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

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

3.2.2 Non-target lesions (NTLs) and new lesions – site investigator data

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

NTL response will be derived based on the investigator's overall assessment of NTLs as follows:

Table 6 NTL Visit Responses

Visit Responses	Description
Complete response (CR)	Disappearance of all NTLs since baseline. All lymph nodes must be non-pathological in size (<10 mm short axis).
Progressive disease (PD)	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy
Non-CR/Non-PD	Persistence of one or more NTL
Not evaluable (NE)	Only relevant when one or some of the NTLs were not assessed and, in the investigator's opinion, they are not able to provide an evaluable overall NTL assessment at this visit NOTE: for participants without TLs at baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met
Not applicable (NA)	Only relevant if no NTLs present at baseline

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

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

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

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

New lesions will be identified via a Yes/No tick box. The absence and presence of new lesions at each visit should be listed alongside the TL and NTL visit responses.

A new lesion indicates progression so the overall visit response will be PD irrespective of the TL and NTL response.

If the question 'Any new lesions since baseline' has not been answered with Yes or No and the new lesion details are blank this is not evidence that no new lesions are present, but should not overtly affect the derivation.

Symptomatic progression is not a descriptor for progression of NTLs: it is a reason for stopping study therapy and will not be included in any assessment of NTLs.

Participants with 'symptomatic progression' requiring discontinuation of treatment without objective evidence of disease progression at that time should continue to undergo tumour assessments where possible until objective disease progression is observed.

3.2.3 Overall visit response – site investigator data

Table 7 defines how the previously defined TL and NTL visit responses will be combined with new lesion information to give an overall visit response.

Table 7 Overall visit responses

Target lesions	Non-target lesions	New lesions	Overall visit response
CR	CR	No	CR
CR	NA	No	CR
NA	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	NE	No	PR
PR	Non-PD or NE or NA	No	PR
SD	Non-PD or NE or NA	No	SD
NA	Non-CR/Non-PD	No	SD (Non-CR/Non-PD)
NE	Non-PD or NE or NA	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; NA, not applicable (only relevant if there were no target lesions at baseline or no non target lesions at baseline); NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease; TL, target lesion.

3.2.4 Independent review

A planned BICR of all radiological imaging data will be carried out using RECIST version 1.1. All radiological scans for all participants (including those at unscheduled visits, or outside visit windows) will be collected on an ongoing basis and sent to Parexel Informatics for central analysis. For each participant, the BICR will define the overall visit response (i.e. the response obtained overall at each visit by assessing TLs, NTLs and new lesions) data and no programmatic derivation of visit response is necessary. (For participants with TLs at baseline: CR, PR, SD, PD, NE; for participants with NTLs only: CR, SD, PD, NE). If a participant has had a tumour assessment that cannot be evaluated, then the participant will be assigned a visit response of NE (unless there is evidence of progression in

which case the response will be assigned as PD). RECIST assessments/scans contributing towards a particular visit may be performed on different dates and for the central review the date of progression for each reviewer will be provided based on the earliest of the scan dates of the component that triggered the progression.

If adjudication is performed, the reviewer that the adjudicator agreed with will be selected as a single reviewer (note in the case of more than one review period, the latest adjudicator decision will be used). In the absence of adjudication, the records for all visits for a single reviewer will be used. The reviewer selected in the absence of adjudication will be the reviewer who read the baseline scan first. The records from the single selected reviewer will be used to report all BICR RECIST information including dates of progression, visit response, censoring and changes in target lesion dimensions. Endpoints (of ORR, PFS, DCR and DoR) will be derived programmatically from this information.

Results of this independent review will not be communicated to investigators and the management of participants will be based solely upon the results of the RECIST 1.1 assessment conducted by the investigator.

A BICR of all participants will be performed up to the primary database lock, which will cover all of the scans up to the DCO. After the primary analysis DCO, images will no longer need to be collected centrally. Ongoing collection of site reviewed tumour assessment is required and must be recorded in the eCRF. Radiological examinations performed in the conduct of this study should be retained at site as source data.

Further details of the BICR will be documented in the BICR Charter.

3.3 Efficacy Variables

3.3.1 Objective Response Rate

The ORR is defined as follows:

- The ORR is the proportion (%) of participants with measurable disease at baseline who have a confirmed complete response (CR) or partial response (PR), as determined by BICR per RECIST v1.1. The denominator is defined as the subset of all treated participants with measurable disease at baseline per BICR.

ORR will also be defined similarly based on site investigator assessments. The denominator for investigator assessment based ORR is defined as the subset of all treated participants with measurable disease at baseline per investigator.

Data obtained up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of the ORR. Responses that occur after the start of subsequent anti-cancer therapy must be excluded from the derivation of ORR (ie, only responses that occur prior to receiving subsequent therapy will be included in the numerator). Radiotherapy is not considered as subsequent cancer therapy while calculating ORR.

A confirmed response of CR/PR means that a response of CR/PR is recorded at 1 visit and confirmed by repeat imaging not less than 4 weeks after the visit when the response was first observed with no evidence of progression between the initial and CR/PR confirmation visit. Summaries of ORR for the primary analysis will be based on BICR.

3.3.2 Best Objective Response

Best objective response (BoR) is calculated based on the overall visit responses from each RECIST assessment, described in Section 3.2. It is the best response a participant has had following first treatment administration, but prior to starting any subsequent cancer therapy and up to and including RECIST progression or the last evaluable assessment in the absence of RECIST progression. Categorisation of BoR will be based on RECIST using the following response categories: CR, PR, SD, NED (applies only to those participants entering the study with no disease at baseline), PD and NE.

CR or PR must be confirmed. For CR/PR, the initial overall visit assessment which showed a response will use the latest of the dates contributing towards a particular overall visit assessment.

For determination of a best response of SD, the earliest of the dates contributing towards a particular overall visit assessment will be used. SD should be recorded at least 6 weeks minus 1 week, i.e. at least 35 days (to allow for an early assessment within the assessment window), after first dose of study treatment.

BoR will be determined programmatically based on RECIST from the overall visit response using all BICR data up until the first progression event. It will also be determined programmatically based on RECIST using all site investigator data up until the first progression event. The denominators for each case will be consistent with those used in the ORR analysis.

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

For participants who die with no evaluable RECIST assessments, if the death occurs ≤ 49 days (i.e. 6 weeks + 1 week to allow for a late assessment within the assessment window) after first dose, then BoR will be assigned to the progression (PD) category. For participants who die with no evaluable RECIST assessments, if the death occurs > 49 days after start of treatment then BoR will be assigned to the NE category.

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

3.3.3 Duration of Response

DoR is defined as the time from the date of first documented response (which is subsequently confirmed) until the first date of documented progression or death in the absence of disease progression

- DoR = (date of PFS event or censoring) – (date of start of response) +1

The end of response should coincide with the date of progression or death from any cause used for the PFS endpoint (see Section 3.3.5). The time of the initial response will be defined as the latest of the dates contributing towards the first visit that was CR or PR that was subsequently confirmed. If a

participant does not progress following a response, then their DoR will use the PFS censoring time. Duration of response will be presented in months.

3.3.4 Depth of Response

Depth of response is defined as the best percentage change from baseline in Target Lesions.

The absolute change and percentage change from baseline in the sum of tumour size at each assessment will be calculated. Tumour size is the sum of the longest diameters of the TLs.

Percent changes in tumour size from baseline will be determined for participants with measurable disease at baseline and is derived at each visit as percent change in the sum of the diameters of TLs.

- % change = [(post baseline TL sum – baseline TL sum) / baseline TL sum] *100.

The best change in tumour size (i.e. depth of response) is the largest decrease from baseline or the smallest increase from baseline in the absence of a reduction and will include all assessments prior to the earliest of death in the absence of progression, any evidence of progression, the start of subsequent anti-cancer or the last evaluable RECIST assessment if the participant has not died, progressed or started subsequent anti-cancer therapy.

Baseline for RECIST v1.1 is defined as the last evaluable assessment prior to the start of treatment. If a participant with missing baseline data, best percentage change from baseline will be kept as missing. If best percentage change cannot be calculated due to missing data, a value of +20% will be imputed as the best percentage change from baseline in the following situations (otherwise best percentage change will be left as missing):

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

3.3.5 Progression-Free Survival (PFS)

Progression-free survival is defined as the time from the date of first dose until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the participant discontinues adavosertib or receives another anticancer therapy prior to progression.

- PFS (days) = (date of PFS event or censoring) – (date of first dose of adavosertib) + 1.

Participants who have not progressed or died at the time of analysis will be censored at the date of their last evaluable RECIST v1.1 assessment.

If the participant progresses or dies after 2 or more missed visits, the participant will be censored at the date of the latest evaluable RECIST v1.1 assessment prior to the missed visits.

If the participant has no evaluable visits or does not have baseline data, he/she will be censored at Day 1 unless he/she dies within 2 visits of baseline, in which case the date of death is the event date.

Given the scheduled visit assessment scheme (i.e. six-weekly for the first 48 weeks and then nine-weekly thereafter) the definition of 2 missed visits will change.

1. If the previous RECIST assessment is <= study day 35 (i.e. week 5) then two missing visits will equate to 13 weeks since the previous RECIST assessment, allowing for a late visit (i.e. 2 x 6 weeks + 1 week for a late assessment = 13 weeks).
2. If the previous RECIST assessment is >35 and < study day 287 (i.e. week 41) then two missing visits will equate to 14 weeks since the previous RECIST assessment, allowing for early and late visits (i.e. 2 x 6 weeks + 1 week for an early assessment + 1 week for a late assessment = 14 weeks).
3. If the two missed visits occur over the period when the scheduled frequency of RECIST assessments changes from six-weekly to nine-weekly this will equate to 17 weeks (i.e. take the average of 6 and 9 weeks which gives 7.5 weeks and then apply same rationale, hence 2 x 7.5 weeks + 1 week for an early assessment + 1 week for a late assessment = 17 weeks). The time period for the previous RECIST assessment will be from study days 288 to 329 (i.e. week 41 to week 47).
4. From week 47 onwards (when the scheduling changes to nine-weekly assessments), two missing visits will equate to 20 weeks (i.e. 2 x 9 weeks + 1 week for an early assessment + 1 week for a late assessment = 20 weeks).

3.3.6 Progression-Free Survival at 6 months (PFS6)

PFS6 is the proportion of participants alive and progression-free at 6 months (PFS6). It is defined as the Kaplan-Meier estimate of PFS (per RECIST v1.1) at 6 months.

3.3.7 Overall Survival

The Overall Survival (OS) is defined as the time from the date of first dose of adavosertib until death due to any cause, regardless of whether the participant discontinues adavosertib or receives another anticancer therapy.

- OS (days) = (date of death or censoring) – (date of first dose of adavosertib) + 1

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

The date that an individual participant was last known to be alive will be identified using the data recorded within the SURVIVE and DEATH modules of the eCRF.

Note: Survival calls will be made in the week following the date of DCO for the analysis, and if participants are confirmed to be alive or if the death date is after the DCO date these participants will be censored at the date of DCO. The status of ongoing, withdrawn (from the study) and “lost to follow-up” participants at the time of the primary 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.

It may be necessary to use all relevant CRF fields to determine the last recorded date on which the patient was known to be alive for those patients still on treatment. The last date for each individual patient is defined as the latest among the following dates recorded on the case report forms (CRFs):

- AE start and stop dates

- Admission and discharge dates of hospitalization
- Study treatment date
- End of treatment date
- Laboratory test dates
- Date of vital signs
- Disease assessment dates on RECIST CRF
- Start and stop dates of alternative anticancer treatment
- Date last known alive on survival status CRF
- End of study date

3.3.8 Disease control rate

Disease control rate is defined as the proportion of participants with best response of confirmed CR, confirmed PR, or who have stable disease at least 5 weeks after first dose (to allow for an early assessment within the assessment window).

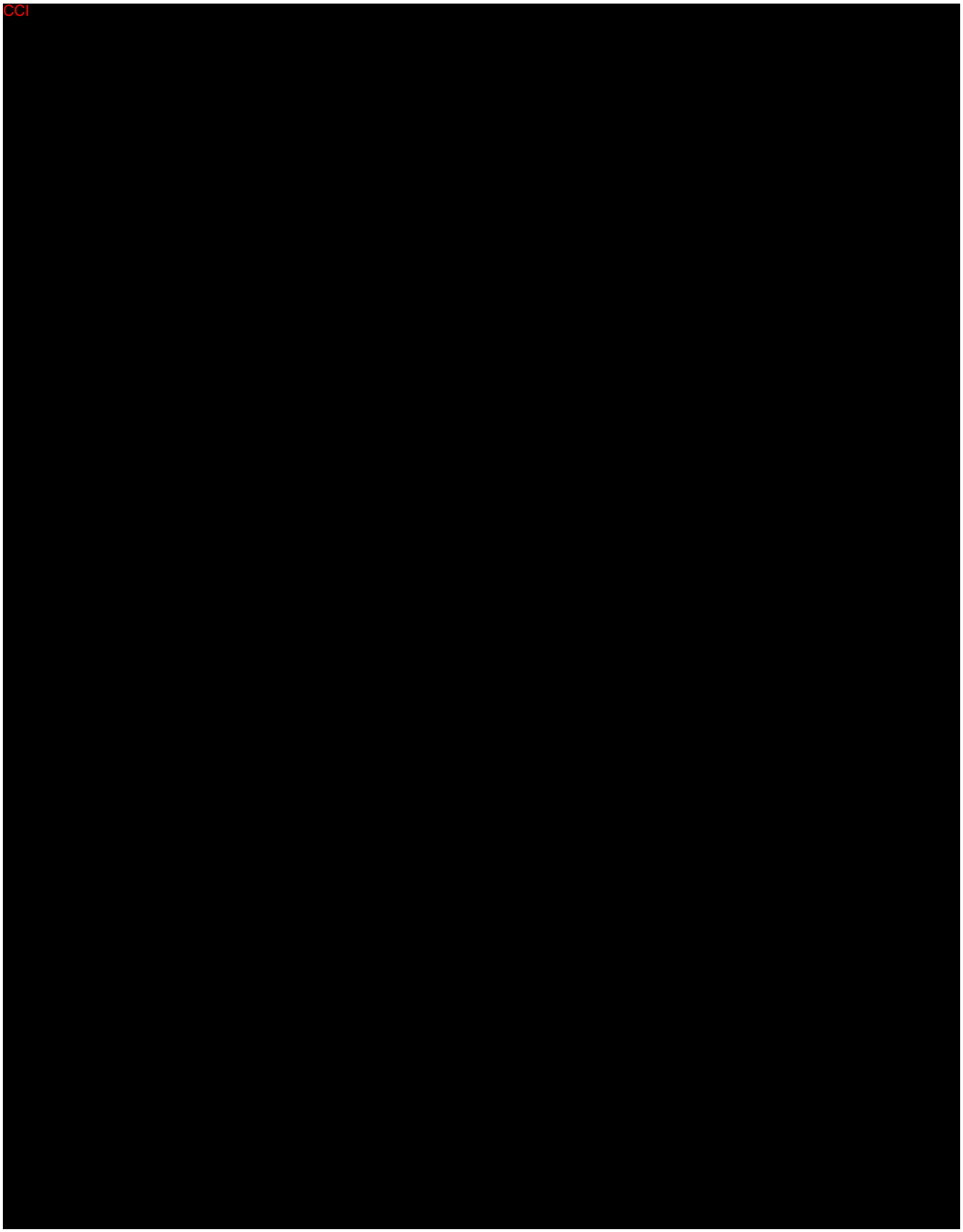
3.4 CCI

CCI

3.4.1 CCI

CCI

CCI



CCI

[redacted]

3.4.2 CCI

CCI

[redacted]

CCI

3.4.3 CCI

CCI

CCI

3.4.4 CCI

CCI

3.5 Other Variables

3.5.1 Prior and Concomitant Medications and Therapies

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

- Prior medications are those taken prior to study treatment with a stop date prior to the first dose of study treatment.

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

Missing start and stop dates for medications will be imputed using the rules described in Section 4.1.1.

3.6 Safety Variables

Safety and tolerability will be evaluated in terms of AEs, vital signs, clinical laboratory assessments, ECGs, and AEs leading to dose interruptions, dose reductions, and dose discontinuations.

3.6.1 Exposure and dose interruptions

The total and actual exposure calculations make no adjustment for any dose reductions that may have occurred.

Exposure will also be measured by the number of cycles received. A cycle corresponds to a period of 21 days. If a cycle is prolonged due to toxicity, it should still be counted as one cycle. A cycle will be counted if treatment is started even if the full dose is not delivered.

3.6.1.1 Dose calculations

Duration of adavosertib exposure (or intended) is calculated as follows:

- Total (or intended) exposure = min (last dose date where dose > 0 mg, date of death, date of data cut off) – first dose date + 1

Actual exposure of study treatment

- Actual exposure = intended exposure – total duration of dose interruptions, where intended exposure will be calculated as above and a dose interruption is defined as any length of time where the participant has not taken any of the planned dose.

Number of treatment cycles received

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

Missed or forgotten doses

- Missed and forgotten doses should be recorded on the exposure form as a dose interruption with the reason recorded as “Patient forgot to take dose”. These missed or forgotten doses will not be included as dose interruptions in the summary tables but the information will appear in the listing for dosing. However, these missed and forgotten doses will be considered in the derivation of actual exposure.

Participants who permanently discontinue during a dose interruption

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

3.6.1.2 Dose Intensity

Dose intensity will be addressed by considering relative dose intensity (RDI). and percentage intended dose (PID).

- Relative dose intensity (RDI) is the percentage of the actual dose delivered relative to the intended dose through to treatment discontinuation. This is derived as:
  - RDI = 100% * d/ D_c, 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_c is the intended cumulative dose up to the earlier of progression (or a censoring event) or the actual last day of dosing.
- Percentage intended dose (PID) is the percentage of the actual dose delivered relative to the intended dose through to progression. The PID is derived as:
  - PID= 100% * d/D_p, where d is the actual cumulative dose delivered up to progression (or a censoring event). D_p is the total dose that would be delivered, if there were no modification to dose or schedule.

Please note the calculation of D_c and D_p will not change when investigator modified the dose level of individual participants. If a participant received the planned dose at the scheduled time at every cycle, then RDI = 1.

3.6.2 Adverse events

Details of all AEs and SAEs will be collected for a participant from the signing of the Informed Consent Form (ICF) up to 30 days after the last dose of adavosertib. If an event starts after this period and the Investigator considers that it is possible that it is due to a late onset toxicity to adavosertib, then it should be reported as an AE or SAE.

All AEs will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) providing the System Organ Class (SOC) and Preferred Term (PT).

In addition, all AEs will also be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for AEs (CTCAE Version 5.0) allocating grades from Grade 1 to Grade 5 which will be used for the reporting. The meaning of these categories are as follows:

- Grade 1: Mild AE
- Grade 2: Moderate AE
- Grade 3: Severe AE
- Grade 4: Life-threatening or disabling AE
- Grade 5: Death related to AE

Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs and ECG abnormalities should therefore only be reported as AEs if they fulfil any of the SAE criteria, are the

reason for discontinuation of treatment with the investigational product or are considered to be clinically relevant as judged by the investigator.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in nonmandated 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.

Treatment Emergent Adverse Events

The following events will be considered treatment emergent:

- Adverse events with an onset date on or after first dose of adavosertib and within 30 days after last dose of adavosertib
- Worsening of pre-existing events on or after first dose of adavosertib and within 30 days after last dose of adavosertib. Latest grade prior to first dose will be considered as the baseline of pre-existing events.

Missing start and stop dates for AEs will be imputed using the rules described in Section 4.1.1.

3.6.3 Hy's law

Cases where a participant shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3 x ULN together with total bilirubin ≥ 2 x ULN will need to be reported as SAEs if criteria are met for a Potential Hy's Law case. Please refer to Protocol Appendix H for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

3.6.4 ECG changes

These measurements will be recorded as detailed in the study schedule (See Appendix A).

At Screening, and as clinically indicated throughout the study, ECGs will be obtained after the participant has been in a supine position for at least 10 minutes and recorded while the participant remains in that position. Any clinically significant abnormalities detected require triplicate ECG results. At each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained in succession, within 5 minutes. If there is a clinically significant abnormal unscheduled ECG finding during the treatment period, this should be recorded as the AE.

3.6.5 Vital sign changes

Vital signs will be collected as outlined in Appendix A. Measurements will include SBP (mmHg), DBP (mmHg), pulse rate, heart rate (bpm) and body temperature (degrees Celsius). Change from baseline in vital signs variables will be calculated for each post-dose visit on treatment. For derivation of post-baseline visit values, considering visit window, and handling multiple records, derivation rules as described in section 3.1 will be used.

3.6.6 Laboratory data

Laboratory data (clinical chemistry, haematology and urinalysis) will be collected as detailed in the Schedule of Assessment (Appendix A). Coagulation and urinalysis will be collected at screening and as clinically indicated. Haematology and clinical chemistry parameters will be collected at screening, at Day 1 and Day 8 of each cycle, at study treatment discontinuation, 30 days after last dose and at other times if clinically indicated. For the definition of baseline and the derivation of post baseline visit values considering visit windows and how to handle multiple records, derivation rules as described in section 3.1 will be used.

Women of childbearing potential must have a negative urine or serum pregnancy test during screening and a confirmatory negative test prior to dosing on Day 1 of each treatment cycle. In the event of suspected pregnancy during the study, the test should be repeated prior to dosing and, if positive, the participant discontinued from study treatment immediately.

The laboratory parameters presented in Table 9 will be measured as a minimum.

Table 9 Laboratory Safety Variables

Haematology	**Clinical Chemistry**
B-Haemaglobin	S/P-Albumin
B-Leukocyte	S/P-Alanine aminotransferase (ALT)
B-Haematocrit	S/P-Aspartate aminotransferase (AST)
B-Red blood cell count	S/P-Alkaline phosphatase (ALP)
B-Absolute leukocyte differential count	S/P-Bilirubin, total
B-Neutrophils	S/P-Calcium, total
B-Lymphocytes	S/P-Creatinine
B-Monocytes	S/P-Chloride
B-Basophils	S/P-Potassium
B-Eosinophils	S/P-Sodium
B-Platelet counts	S/P-Urea nitrogen or blood urea nitrogen
B-Absolute neutrophil count	
Coagulation	**Pregnancy test (blood or urine)**
B-PT or INR with PTT	

Urinalysis	
U-Hb/erythrocytes/blood	
U-Protein/albumin	
U-Glucose	

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; B, blood; Hb, haemoglobin; INR, International Normalised Ratio; P, plasma; PT, prothrombin time; PTT, partial thromboplastin time; S, serum; U, urine.

Laboratory data will be from local laboratories and units will be entered into the CRF. The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities.

Change from baseline in clinical chemistry and haematology variables will be calculated for each post-dose visit on treatment.

Absolute values will be compared to the local reference range and classified as low (below range), normal (within range or on limits of range) and high (above range). As applicable, values will be converted to standard units. The assessment of haematology, clinical chemistry and coagulation that deviate above or below the normal range will be classified by Common Terminology Criteria (CTC) grade (NCI CTCAE v5) taking values: Grade 0, 1, 2, 3, or 4.

The maximum (or minimum) on-treatment value (depending on the direction of an adverse effect) will be defined for each laboratory parameter as the maximum (or minimum) post-dose value up until treatment discontinuation.

3.6.7 ECOG Performance Status

ECOG PS will be assessed at the times specified in the schedule of assessments (Appendix A) based on the following:

0. Normal activity. Fully active, able to carry out all usual activities without restrictions

1. Symptoms, but ambulatory. Restricted in strenuous activity, but ambulatory and able to carry out work of a light or work of sedentary nature (eg, light housework or office work)

2. In bed <50% of the time. Ambulatory and capable of self-care, but unable to carry out any work activities; up and about more than 50% of waking hours

3. In bed >50% of the time. Capable of only limited self-care; confined to bed or chair more than 50% of waking hours

4. 100% bedridden. Completely disabled. Cannot carry on any self-care and totally confined to bed or chair

5. Dead.

Any significant change from baseline or screening must be reported as an AE.

3.7 Pharmacokinetic Variables

3.7.1 Pharmacokinetics

Blood sample for measurement of plasma concentration will be collected as the following timepoints:

- Cycle 1, Day 5 (-1 day): pre-dose and 2 hours post-dose
- Cycle 2, Day 5 (-1 day): pre-dose and 2 hours post-dose

All PK samples need to be collected within 10% of the nominal time (± 6 minutes for a 60-minute sample) to be protocol compliant. Pre-dose samples should be collected within 60 minutes prior to dosing. Samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor (eg, for safety reasons).

Pharmacokinetic parameters will be estimated from the plasma concentration data by Covance Pharmacokinetic Alliance (CPKA). The following PK parameters will be determined at cycle 1 day 5 and cycle 2 day 5 (steady-state): C_{max} and C_{trough} (as data allows).

C_{max} and C_{trough}, will be obtained directly from the observed plasma concentration.

4 ANALYSIS METHODS

4.1 General Principles

Continuous data will be summarized in terms of the mean, standard deviation (SD), median, minimum, maximum and number of observations, unless otherwise stated. Continuous data that are expected to be skewed will be presented in terms of the maximum, upper quartile, median, lower quartile, minimum and number of observations. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median, lower quartile and upper quartile will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic.

Categorical data will be summarized in terms of the number of participants providing data at the relevant time point (n), frequency counts and percentages.

Percentages will be presented to one decimal place. Unless otherwise stated, percentages will be calculated out of the population total. Percentages will not be presented for zero counts.

Exact CIs for proportions will be calculated using the Clopper-Pearson method.

For percentiles of survival times based on the Kaplan-Meier method (eg, median survival), CIs will be calculated using the default method available in the SAS LIFETEST procedure (ie, the Klein and Moeschberger extension of the Brookmeyer-Crowley method).

For point-estimates of survival based on the Kaplan-Meier method (eg, for PFS6), CIs will be calculated using the default method available in the SAS LIFETEST procedure (ie, using Greenwood's estimate of standard error and a log-log transformation).

Confidence intervals will be presented to one more decimal place than the raw data.

Due to Covid-19 some participants were screen failed in the first instance but later rescreened. For summary tables only data from the rescreening will be presented for the rescreened participants. For listings both original screen failure data and rescreened data will be presented for the rescreened participants.

4.1.1 Handling of Dropouts or Missing Data

Summary statistics will be based on non-missing values. Missing safety data will generally not be imputed. However, safety assessment values (vital signs, laboratory assessments) of the form of "<x" (ie, below the lower limit of quantification) or >x (ie, above the upper limit of quantification) will be imputed as "x" in the calculation of summary statistics but displayed as "<x" or ">x" in the listings.

For missing diagnostic dates, if day and/or month are missing use 01 and/or Jan. If year is missing, put the complete date to missing.

For missing or partial missing start dates for AEs and concomitant medications/procedures, the following will be applied:

- Missing day - Impute the 1st of the month unless month and year are same as month and year of first dose of study drug then impute first dose date
- Missing day and month – impute 1st January unless year is the same as first dose of study drug then impute first dose date.
- Completely missing date – impute to first dose date unless the end date is less than the first dose date, in which case impute to 1st January of the same year as the end date.

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

For missing or partial missing stop dates of AEs or concomitant medications/procedures, the following will be applied:

- Missing day - Impute the last day of the month unless month is the same as month of the last dose of study drug then impute last dose date.
- Missing day and month – impute 31st December unless year is the same as last dose date then impute last dose date.
- Completely missing date - Impute the stop dates of AEs to the date of cut-off for the patients with AE still is on-going, when the date of cut-off applies to the analysis. Do not impute it for the all the other situation.

For missing first dosing time for exposure data, impute the first dosing time as 00:00. For missing last dosing time for exposure data, impute the last dosing time as 23:59.

The imputation of dates will be used to decide if an observation is treatment emergent for adverse events or concomitant medications. The imputed dates are not used to calculate durations.

It is not expected to have missing dates for unscheduled laboratory, ECG, diagnostics data. However, if there are missing dates, for any derivations, the dates should be imputed following the rules for concomitant medications and AEs

If a participant is known to have died where only a partial death date is available then the date of death will be imputed as the latest of the last date known to be alive +1 from the database and the death date using the available information provided:

- For Missing day only – using the 1st of the month
- For Missing day and Month – using the 1st of January

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

4.2 Analysis Methods

4.2.1 Disposition, Demography and Baseline Characteristics

4.2.1.1 Participant Disposition

A clear accounting of the disposition of all participants who enter the study will be provided, from screening to study completion.

The following participant disposition summaries will be produced:

- The number and percentage of participants, enrolled participants (i.e. those providing informed consent), and who received adavosertib will be summarised for all participants.
- Discontinuation from adavosertib and/or discontinuation from study, together with reason for discontinuation (including the reason due to COVID-19 pandemic) will be summarised using the FAS.

4.2.1.2 Analysis Sets

The following summaries will be provided:

- A summary of the number and percentage of participants in each analysis set. Exclusions from each analysis population will also be summarized by reason.

By-participant listings of participants excluded from each analysis set will be provided.

4.2.1.3 Protocol Deviations

Programmable PDs will be detected from the data recorded in the clinical database and will be reviewed at regular PD review meetings. At this meeting, the programmatically derived PDs will be checked to ensure that they have been correctly classified as important or not important PDs.

On an ongoing basis throughout the study, monitoring notes or summaries will also be reviewed to determine any important post-entry deviations that are not identifiable via programming.

The final classification of IPDs will be made prior to database lock (DBL) or data cut-off for primary analysis. The number and percentage of participants with important protocol deviations in each deviation category, Number of subjects with at least 1 COVID-19 related important protocol deviation and Number of subjects with at least 1 important protocol deviation, excluding COVID-19 related IPDs will be summarized. Important protocol deviations will be listed. Any other relevant deviations from monitoring notes or reports will be reported in the CSR as required.

4.2.1.4 Demography and baseline characteristics

Demographic and other baseline characteristics will be listed for all participants and summarised for the FAS, as:

- Demographics (age (years), age group [<50, ≥50-< 65, ≥65-<75, and ≥75 years], sex, race (if collected) and ethnicity)

- Participant characteristics at baseline (height (cm), weight (kg), weight groups [<40, ≥40-< 75, ≥75-<90, ≥90-<120, and ≥120 kg], body mass index (BMI), and BMI groups [Underweight (<18.5), Normal weight (=18.5 - <25.0), Overweight (=25.0 - <30.0), Obese (≥30.0)]

- A summary and a list of participants by country will be provided.

4.2.1.5 Disease diagnosis and staging

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

- Primary Tumour Location
- Histology Type
- Primary Tumour
- Regional Lymph Nodes
- Distant Metastases
- Tumour Grade
- International Federation of Gynecology and Obstetrics (FIGO) Stage

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

- Site of local/metastatic disease
- Metastatic/Locally Advanced

- ECOG performance status

4.2.1.6 Prior therapies

The following categorical summaries will be presented for all participants in the FAS:

- The number and percentage of participants with prior therapy class will be summarised by category (e.g. immunotherapy, Hormonal, etc.).
- Number of regimens
- Treatment Status
- Treatment Outcome
- Oncology Response Assessment Result

4.2.1.7 Concomitant medications

Concomitant medications and procedures will be listed for all participants in the FAS.

World Health Organization (WHO) Drug Global Mar 2020, B3 will be used for coding medication terms.

Partial dates will be handled as follows to determine whether a medication is treatment emergent: Missing day only (assume Day 1 of each respective month), missing day and month (assume 1st January unless year is the same as first dose date then impute first dose date), completely missing (assume first dose date unless the end date suggests it could have started prior to this in which case impute the 1st January of the same year as the treatment start date). Imputed dates are not to be used to calculate durations.

Concomitant medications will be summarized (frequency and percentage of participants) by ATC dictionary text and generic term. Each unique drug will be counted once per participant. The summary will be ordered by decreasing total frequency of use. Disallowed concomitant medications and all-allowed concomitant medications will be summarized in the same table with * to indicate the disallowed concomitant medications.

A by-participant listing of all medications will be provided.

4.2.1.8 Medical history

Medical history and relevant surgical history will be coded using MedDRA version 23.0 or later version. The frequency and percentage of participants with each condition will be summarised by SOC and PT. Participants with multiple unique terms will be counted once per each unique PT and unique SOC. Each summary will be sorted alphabetically by SOC and PT.

4.2.2 Tumour response and efficacy

Tumour assessments using computed tomography (CT)/magnetic resonance imaging (MRI) will be performed at the times specified in the schedule of assessment (Appendix A). These will be every 6 weeks (±7 days) for the first 48 weeks, then every 9 weeks (±7 days) thereafter until radiological progression. RECIST 1.1 measurements as assessed by the Investigator will be used to derive the primary variable of ORR, and secondary variables of PFS, PFS6 and DOR. The categorisation of objective tumour response assessment into complete response (CR), partial response (PR), stable

disease (SD), progressive disease (PD) or not evaluable (NE) will be based on RECIST 1.1. Summaries for the primary analysis will be based on the BICR.

All RECIST assessments, whether scheduled or unscheduled, and regardless of whether a participant discontinues adavosertib treatment or receives another anti-cancer therapy will be included in the calculation of the efficacy variables.

All efficacy analyses will be performed separately in the FAS and CCAS.

4.2.2.1 Objective Response Rate and Best Objective Response

Summaries of ORR for the primary analysis will be based on BICR. ORR and its 90% and 95% CI (Clopper-Pearson) will be summarised. ORR per investigator review will be a sensitivity analysis.

ORR and number of participants with a confirmed response of CR or PR will be analysis at interim data cut off and primary data cut off.

Best objective response (BoR) will be summarised by n (%) for each category (CR, PR, SD, PD and NE). No formal statistical analyses are planned for BoR.

All summaries of ORR and BoR will be performed in the FAS and CCAS separately.

4.2.2.2 Duration of Response

If there are sufficient numbers of responders, and sufficient numbers of responders that have progressed by the point of the analysis, Kaplan-Meier plots of DoR in the responding participants will be produced, and appropriate descriptive summary statistics will be presented (n, number of responses that have progressed or died, median, quartile, minimum and maximum DoR).

Summaries of DoR will be based on BICR; DoR per investigator review will be a sensitivity analysis.

Kaplan-Meier plots, summaries of DoR will be performed in the FAS and CCAS separately.

4.2.2.3 Depth of Response

Depth of response will be summarised using descriptive statistics. Waterfall plots showing the best percentage change from baseline in sum of the diameters of TLs will be produced. Spider plots showing the percentage change from baseline in tumour size for each participant over time will be produced.

Summaries of percentage change from baseline will be based on BICR.

Summaries and plots of depth of response will be performed in the FAS and CCAS separately.

4.2.2.4 Progression-free Survival

Summaries of PFS (n, events, medians, quartiles, proportion progression free at 3, 6, 9 and 12 months and corresponding 95% CIs) and Kaplan-Meier plots will be provided.

Summaries of PFS will be based on BICR; PFS per investigator review will be a sensitivity analysis.

Summaries and plots of PFS will be performed in the FAS and CCAS separately.

4.2.2.5 Progression-free survival at 6 months

The proportion of participants alive and progression free at 6 months (PFS6) will be defined as the Kaplan-Meier estimate of PFS (per RECIST v1.1) at 6 months.

Summaries of PFS6 will be based on BICR; PFS6 per investigator review will be a sensitivity analysis.

4.2.2.6 Overall survival

Summaries of OS (n, events, medians, quartiles, proportion alive at 3, 6, 9 and 12 months and corresponding 95% CIs) and a Kaplan-Meier plot will be provided.

Summaries and plots of OS will be performed in the FAS and CCAS separately.

4.2.2.7 Disease control rate

DCR and its 95% CI (Clopper-Pearson) will be summarised. Summaries of DCR will be based on BICR; DCR per investigator review will be a sensitivity analysis.

Summaries of DCR will be performed in the FAS and CCAS separately.

4.2.3 CCI

4.2.3.1 CCI

CCI

CCI [redacted]

4.2.3.2 CCI [redacted]

CCI [redacted]

4.2.3.3 CCI [redacted]

CCI [redacted]

4.2.4 Safety Analyses

Safety analyses will be performed using the FAS. Safety data will be presented using descriptive statistics unless otherwise specified.

4.2.4.1 Exposure

Exposure to adavosertib will be summarised in the following ways:

- Duration of adavosertib exposure (months)
- Total number of initiated cycles
- Cumulative actual dose of adavosertib (mg)
- Actual exposure to adavosertib (months)
- Relative dose intensity of adavosertib (%)
- Dose interruptions
- Dose reductions
- Dose discontinuations

Listings of treatment administration and treatment modifications will be provided.

4.2.4.2 Adverse Events/Serious Adverse Events

Adverse events will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA).

AEs will be presented by System Organ Class and/or Preferred Term covering number and percentage of participants reporting at least one event and number of events where appropriate.

AEs occurring prior to start of adavosertib and treatment emergent AEs will be presented separately.

An overview of AEs will present the number and percentage of participants with any AE, AEs with outcome of death, serious AEs, and AEs leading to discontinuation of adavosertib, as well as AEs

leading to adavosertib dose interruptions, AEs leading to adavosertib dose reduction and AEs leading to withdrawal from study as well as the number of individual occurrences in those categories.

Separate AE tables will be provided taking into consideration relationship as assessed by the investigator, CTC grading, seriousness, death and events leading to discontinuation of adavosertib as well as other action taken related to adavosertib, and timing of events.

An additional table will present number and percentage of participants with most common AEs. Most common (eg, frequency of >5%).

In accordance with the requirements of the FDA, a separate table will present non-serious AEs occurring in more than 5% of participants.

Key subject information will be presented for participants with AEs with outcome of death, serious AEs, and AEs leading to discontinuation of IP.

An AE listing for the safety analysis set will cover details for each individual AE.

Participants with multiple events in the same category are counted only once in that category. Participants with events in more than 1 category are counted once in each of those categories. Each participant is represented with the maximum reported intensity only for each preferred term. Each participant is represented by the maximum reported relationship for each preferred term.

Any AE occurring within the defined follow-up period after discontinuation of IP will be included in the AE summaries. Any AEs in this period that occur after a participant has received further therapy for cancer (following discontinuation of IP) will be flagged in the data listings. Adverse events occurring after the 30-day follow-up period after discontinuation of IP will be listed separately, but not included in the summaries.

4.2.4.3 Electrocardiographic (ECG) data

The listings with ECG overall qualitative conclusion per time point and the abnormal ECG findings will be provided. ECG measurements are taken during screening and as clinically indicated.

4.2.4.4 Vital signs assessment

Systolic and diastolic blood pressure, pulse rate, heart rate, weight and temperature will be collected at Screening and then on Day 1 and Day 8 of each treatment cycle. Measurements will be taken prior to dose administration. Height will only be collected at the screening visit and BMI will be calculated for each visit where weight is assessed.

Summary statistics for continuous variables will include n, mean, SD, Min, Q1, median, Q3, and Max. Observed value, and change from baseline values for each visit-based parameter will be presented.

The number (and percentage) of participants will be presented by laboratory status including change in abnormality (eg. Low, normal, high; abnormal-clinically significant, abnormal – clinically not significant) from baseline to:

- Each scheduled time point

- Maximum on-treatment value
- Minimum on-treatment value
- Maximum post-baseline value
- Minimum post-baseline value

Frequency tables will present the number and percentage of subjects by abnormality status over time (by visit) and the number (and percentage) of subjects with at least one abnormal or clinically significant abnormality.

Supportive vital signs listings will include observed values and change from baseline values, as well as abnormalities.

4.2.4.5 Laboratory data

All laboratory parameters will be summarized based on the FAS.

Assuming laboratory data on C1D1 were performed before first day administration of study therapy, the evaluations collected prior to (and including) C1D1 will be reported as baseline data. The evaluations collected after C1D1 will be reported as on-treatment. All laboratory tables will be restricted to the on-study measurements at protocol specified time points (no unscheduled visits). The laboratory listings will however include all measurements (whether on-treatment or not). If a visit falls outside the protocol specified timepoint, visit windowing as described in Section 3.1.1 will be used.

Laboratory parameters including clinical chemistry and haematology parameters will be presented. Summaries will include the observed value, change from baseline values over time. Summary statistics for continuous variables include the number of participants included in summary, mean, SD, minimum, 1st quartile, median, 3rd quartile and maximum. The CTCAE grade including shift from baseline to maximum post-baseline grade on treatment will be summarised.

The number (and percentage) of participants will be presented by laboratory status including change in abnormality (eg. Low, normal, high; abnormal-clinically significant, abnormal – clinically not significant) from baseline to:

- Each scheduled time point,
- Maximum on-treatment value
- Minimum on-treatment value
- Maximum post-baseline value
- Minimum post-baseline value.

The number (and percentage) of participants in abnormality status or clinically significant abnormalities in laboratory parameters over time will be provided.

The listings (haematology clinical chemistry and urinalysis separately), will include all the laboratory parameters as available in the data base (including laboratory tests codes as “Other”) with the corresponding relevant information. All laboratory data will be listed and values outside the normal ranges will be flagged.

4.2.4.5.1 Hy's Law

Participants with potential Hy's Law will be listed, it includes all participants who have ALT or AST ⩾3 time of upper limit of normal (ULN) together with total bilirubin (TBL) ⩾2 time of ULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP). In this table the value of individual ALT, AST and total bilirubin at each visit together with the upper limit of normal will be displayed.

4.2.4.6 Physical Examination

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

4.2.4.7 ECOG Performance Status

Summaries of ECOG PS data will include all data obtained up until 30 days after the last dose of adavosertib.

A shift table will be produced comparing baseline value to maximum ECOG PS on-treatment value. The outputs will be presented based on the FAS.

4.2.5 Pharmacokinetic data

Blood samples for assessment of AZD1775 pharmacokinetics will be collected pre-dose and 2-hours post-dose on Day 5 for Cycle 1 and Cycle 2 only.

The derived PK parameters C_{max} and C_{trough} will be summarised by cycle, day and time point as appropriate. Concentrations and derived PK parameters will be summarised using descriptive statistics (geometric mean, geometric coefficient of variation, arithmetic mean, SD, minimum, maximum, number of samples/participants).

Concentrations below the lower limit of quantitation (BLQ) will be reported in the following way:

- Individual BLQ concentrations will be reported as NQ (not quantifiable).
- For summary data:
  - If, at a given time point, 50% or less of the concentrations are not quantifiable (NQ), the geomean, coefficient of variation (CV), geoSD, arithmetic mean and standard deviation (SD) will be calculated by substituting the lower limit of quantification (LLOQ) for values which are NQ.
  - If more than 50%, but not all, of the concentrations are NQ, the geomean, CV, arithmetic mean and SD will be reported as not calculable (NC). The maximum value will be reported from the individual data, and the minimum and median will be set as NQ.
  - If all the concentrations are NQ, the geomean and arithmetic mean will be reported as NQ and the CV and SD as NC.

- The number of values below LLOQ will be reported for each time point along with the total number of collected values.

Three values >LLOQ will be required as a minimum for a concentration or PK parameter to be summarised. Two values will be presented as a minimum and maximum with the other summary statistics as NC. The lower limit of quantitation will be reported in the CSR and in PK tables, figures and listings.

4.2.6 Subgroup Analyses

Subgroup analysis will be performed in the subgroup of participants who have previously been exposed to PD-1/PD-L1 inhibitors. Subgroup analysis will perform for interim analysis and primary analysis.. For subgroup analysis, it will present as one separate column along with the overall participants in the tables.

The subgroup results will be provided for following where they are applicable:

Patient disposition

Demography and baseline characteristics

Prior and post anti-cancer treatment

Exposure, including dose modifications (interruption, reduction, discontinuation)

Adverse Events

Laboratory measurements

Vital Signs/ECG/Physical examination, ECOG

Concomitant medications

Objective Response Rate

Duration of Response

Depth of Response

PFS

PFS6

OS

DCR

5 SAFETY REVIEW COMMITTEE

A Safety Review Committee will be formed to review safety data during the study conduct. SRC will include approximately 3 key study investigators, and AstraZeneca study personnel. All clinical data, including safety, tolerability, dose modifications, and available PK data will be reviewed periodically at an appropriate time interval (e.g. 8 weeks). When at least 6 participants have either received $\geqslant$2 cycles of study treatment or have discontinued study treatment due to unacceptable toxicity, the

Safety Review Committee will convene. SRC will be empowered to make recommendations including the option to modify dosing regimen or stop the study.

Full details of SRC procedures and processes are provided in the SRC Charter.

6 INDEPENDENT DATA MONITORING COMMITTEE

The Independent Data Monitoring Committee (IDMC) will meet for the planned interim analysis when approximately 30 participants in the CCAS have had the opportunity to be treated for at least 4 months, to provide a recommendation based on efficacy observed.

The IDMC will review safety data and will make recommendations to continue, amend, or stop the study based on findings. Serious AEs, AEs, and other safety data will be reviewed, and individual and aggregated safety data will be evaluated by the IDMC.

Full details of the IDMC procedure and processes can be found in the IDMC Charter.

7 INTERIM ANALYSIS

An interim analysis is planned after approximately 30 participants in the CCAS have had the opportunity to be treated for at least 4 months. Recruitment will not be paused whilst the participants required for the interim analysis are evaluated. It may be considered futile to continue recruitment into the study if there is CCI probability for the ORR to be greater than CCI

This translates into observing C or fewer responders out of 30 participants; an ORR of CCI which has a 2-sided exact binomial 80% CI of CCI to CCI wherein the upper confidence limit is below CCI

The analysis will be performed on participants who had the opportunity to be treated for at least 4 months. A sensitivity analysis will be performed on all participants who had the opportunity to be treated for at least 4 months, and those with a best overall response of CR, PR, and progressive disease.

8 CHANGES OF ANALYSIS FROM PROTOCOL

Not applicable for this study.

9 REFERENCES

[1] McMeekin DS, Filiaci VL, Thigpen JT, Gallion HH, Fleming GF, Rodgers WH. The relationship between histology and outcome in advanced and recurrent endometrial cancer patients participating in first-line chemotherapy trials: a Gynecologic Oncology Group study. Gynecol Oncol 2007;106:16–22.

[2] Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85(5):365-76.

[3] Greimel E, Nordin A, Lanceley A, Creutzberg CL, van de Poll-Franse LV, Radisic VB, et al. Quality of Life Group. Psychometric validation of the European Organisation for Research and

Treatment of Cancer Quality of Life Questionnaire-Endometrial Cancer Module (EORTC QLQ-EN24). Eur J Cancer 2011;47:183-90.

10 APPENDIX

10.1 Appendix A: Schedule of Assessments

Table 7 Schedule of Assessments for Screening and Treatment Period

	Screen	Cycle 1 and 2					Cycle 3+		Discontinuation	Progression	Post-treatment follow-up	Survival follow-up	Notes	Details in CSP section or appendix
Timing	**-28 to -1**	**Day 1**	**Day 3**	**Day 5**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**If the reason for discontinuation is disease progression, then only the discontinuation visit is required**		**30 days after last dose**	**Every 12 weeks**		
Visit window (days)	**0**	**0**	**±1**	**-1**	**+2**	**±1**	**+3**	**+2**	**+7**	**+7**	**±7**	**±14**	**C1/2 D5 safety labs visit window ±1 days**	
Informed consent	X													Section 5.1 & Appendix C

	Screen	Cycle 1 and 2					Cycle 3+		Discontinuation	Progression	Post-treatment follow-up	Survival follow-up	Notes	Details in CSP section or appendix
Timing	**-28 to -1**	**Day 1**	**Day 3**	**Day 5**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**If the reason for discontinuation is disease progression, then only the discontinuation visit is required**		**30 days after last dose**	**Every 12 weeks**		
Visit window (days)	**0**	**0**	**±1**	**-1**	**+2**	**±1**	**+3**	**+2**	**+7**	**+7**	**±7**	**±14**	**C1/2 D5 safety labs visit window ±1 days**	
Inclusion/exclusion criteria	X												Recheck inclusion and exclusion criteria prior to first dose	Sections 5.1 & 5.2
CCI [redacted]														
	Routine clinical procedures													
Demography	X													Sections 5.1 & 5.2

	Screen	Cycle 1 and 2					Cycle 3+		Discontinuation	Progression	Post-treatment follow-up	Survival follow-up	Notes	Details in CSP section or appendix
Timing	**-28 to -1**	**Day 1**	**Day 3**	**Day 5**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**If the reason for discontinuation is disease progression, then only the discontinuation visit is required**		**30 days after last dose**	**Every 12 weeks**		
Visit window (days)	**0**	**0**	**±1**	**-1**	**+2**	**±1**	**+3**	**+2**	**+7**	**+7**	**±7**	**±14**	**C1/2 D5 safety labs visit window ±1 days**	
Medical/surgical history	X													Sections 5.1 & 5.2
Previous cancer therapy	X													Section 5.2
Concomitant medication	X	At every study visit												Section 6.5
ECOG performance status	X	X					X		X		X			Appendix B
Physical examination	X	X					X		X		X			Section 8.2.1
Vital signs	X	X		X	X	X	X	X	X		X			Section 8.2.2
Height	X													Section 8.2.1

	Screen	Cycle 1 and 2					Cycle 3+		Discontinuation	Progression	Post-treatment follow-up	Survival follow-up	Notes	Details in CSP section or appendix
Timing	**-28 to -1**	**Day 1**	**Day 3**	**Day 5**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**If the reason for discontinuation is disease progression, then only the discontinuation visit is required**		**30 days after last dose**	**Every 12 weeks**		
Visit window (days)	**0**	**0**	**±1**	**-1**	**+2**	**±1**	**+3**	**+2**	**+7**	**+7**	**±7**	**±14**	**C1/2 D5 safety labs visit window ±1 days**	
Weight	X	X					X		X		X			Section 8.2.1
12-lead ECG	X		As clinically indicated											Section 8.2.3
General assessment through phone call			X										Day 3 phone call for AE assessment	Section 8.3.13.3
	Routine safety measurements													
Adverse events	X		At every study visit											Section 8.3 & Appendix E
Pregnancy test (if applicable)	X	X					X				X			Section 8.2.4

	Screen	Cycle 1 and 2					Cycle 3+		Discontinuation	Progression	Post-treatment follow-up	Survival follow-up	Notes	Details in CSP section or appendix
Timing	**-28 to -1**	**Day 1**	**Day 3**	**Day 5**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**If the reason for discontinuation is disease progression, then only the discontinuation visit is required**		**30 days after last dose**	**Every 12 weeks**		
Visit window (days)	**0**	**0**	**±1**	**-1**	**+2**	**±1**	**+3**	**+2**	**+7**	**+7**	**±7**	**±14**	**C1/2 D5 safety labs visit window ±1 days**	
Haematology	X	X		X	X	X	X	X	X		X		C1/2 D5 safety labs visit window ±1 days	Section 8.2.4
Clinical chemistry	X	X		X	X	X	X	X	X		X		C1/2 D5 safety labs visit window ±1 days	Section 8.2.4
Coagulation	X		As clinically indicated											Section 8.2.4
Urinalysis	X		As clinically indicated											Section 8.2.4

	Screen	Cycle 1 and 2					Cycle 3+		Discontinuation	Progression	Post-treatment follow-up	Survival follow-up	Notes	Details in CSP section or appendix
Timing	**-28 to -1**	**Day 1**	**Day 3**	**Day 5**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**If the reason for discontinuation is disease progression, then only the discontinuation visit is required**		**30 days after last dose**	**Every 12 weeks**		
Visit window (days)	**0**	**0**	**±1**	**-1**	**+2**	**±1**	**+3**	**+2**	**+7**	**+7**	**±7**	**±14**	**C1/2 D5 safety labs visit window ±1 days**	
CCI														
FFPE tumour sample	X													Section 8.6.1
CCI														

	Screen	Cycle 1 and 2					Cycle 3+		Discontinuation	Progression	Post-treatment follow-up	Survival follow-up	Notes	Details in CSP section or appendix
Timing	**-28 to -1**	**Day 1**	**Day 3**	**Day 5**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**If the reason for discontinuation is disease progression, then only the discontinuation visit is required**		**30 days after last dose**	**Every 12 weeks**		
Visit window (days)	**0**	**0**	**±1**	**-1**	**+2**	**±1**	**+3**	**+2**	**+7**	**+7**	**±7**	**±14**	**C1/2 D5 safety labs visit window ±1 days**	

CCI [redacted]

	Screen	Cycle 1 and 2					Cycle 3+		Discontinuation	Progression	Post-treatment follow-up	Survival follow-up	Notes	Details in CSP section or appendix
Timing	**-28 to -1**	**Day 1**	**Day 3**	**Day 5**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**If the reason for discontinuation is disease progression, then only the discontinuation visit is required**		**30 days after last dose**	**Every 12 weeks**		
Visit window (days)	**0**	**0**	**±1**	**-1**	**+2**	**±1**	**+3**	**+2**	**+7**	**+7**	**±7**	**±14**	**C1/2 D5 safety labs visit window ±1 days**	

CCI [redacted]

	Screen	Cycle 1 and 2					Cycle 3+		Discontinuation	Progression	Post-treatment follow-up	Survival follow-up	Notes	Details in CSP section or appendix
Timing	**-28 to -1**	**Day 1**	**Day 3**	**Day 5**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**If the reason for discontinuation is disease progression, then only the discontinuation visit is required**		**30 days after last dose**	**Every 12 weeks**		
Visit window (days)	**0**	**0**	**±1**	**-1**	**+2**	**±1**	**+3**	**+2**	**+7**	**+7**	**±7**	**±14**	**C1/2 D5 safety labs visit window ±1 days**	
	Pharmacokinetic measurements													
PK plasma samples				Pre-dose and 2h post-dose										Section 8.5.1
	Imaging and other assessments													
RECIST v1.1 tumour assessments (CT and/or MRI)	X		Every 6 weeks (±7 days) for the first 48 weeks and then every 9 weeks (±7 days) thereafter, from Day 1 to radiological progression by investigator assessment using RECIST v1.1. Participants who discontinue treatment prior to progression should continue to be scanned until progression.											Section 8.1.1 & Appendix A

	Screen	Cycle 1 and 2					Cycle 3+		Discontinuation	Progression	Post-treatment follow-up	Survival follow-up	Notes	Details in CSP section or appendix
Timing	**-28 to -1**	**Day 1**	**Day 3**	**Day 5**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**If the reason for discontinuation is disease progression, then only the discontinuation visit is required**		**30 days after last dose**	**Every 12 weeks**		
Visit window (days)	**0**	**0**	**±1**	**-1**	**+2**	**±1**	**+3**	**+2**	**+7**	**+7**	**±7**	**±14**	**C1/2 D5 safety labs visit window ±1 days**	
Subsequent cancer therapy following discontinuation of study intervention											X	X		Section 8.1.2.1
Survival status												X		Section 8.1.2

CCI

[redacted]

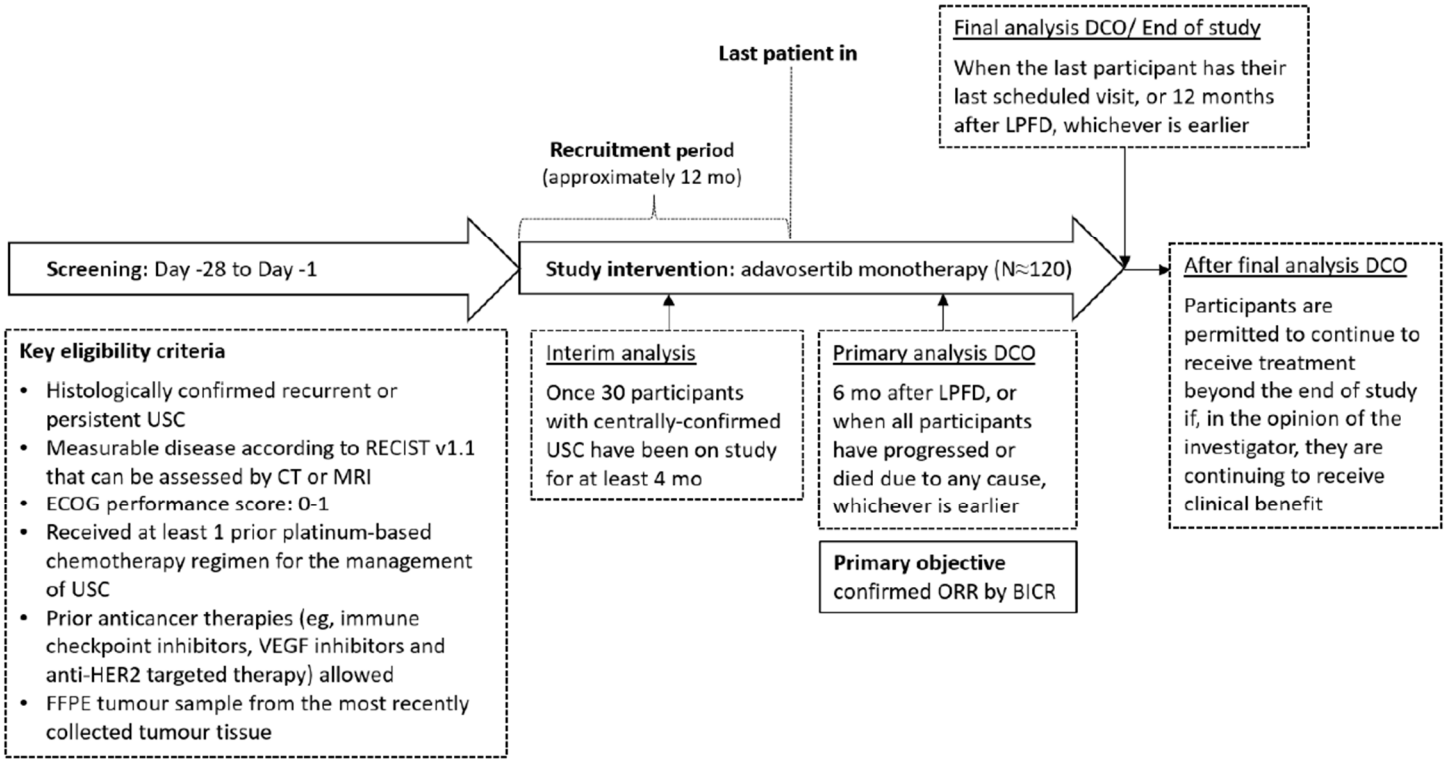
	Screen	Cycle 1 and 2					Cycle 3+		Discontinuation	Progression	Post-treatment follow-up	Survival follow-up	Notes	Details in CSP section or appendix
Timing	**-28 to -1**	**Day 1**	**Day 3**	**Day 5**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**If the reason for discontinuation is disease progression, then only the discontinuation visit is required**		**30 days after last dose**	**Every 12 weeks**		
Visit window (days)	**0**	**0**	**±1**	**-1**	**+2**	**±1**	**+3**	**+2**	**+7**	**+7**	**±7**	**±14**	**C1/2 D5 safety labs visit window ±1 days**	
CCI [redacted]														

	Screen	Cycle 1 and 2					Cycle 3+		Discontinuation	Progression	Post-treatment follow-up	Survival follow-up	Notes	Details in CSP section or appendix
Timing	**-28 to -1**	**Day 1**	**Day 3**	**Day 5**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**If the reason for discontinuation is disease progression, then only the discontinuation visit is required**		**30 days after last dose**	**Every 12 weeks**		
Visit window (days)	**0**	**0**	**±1**	**-1**	**+2**	**±1**	**+3**	**+2**	**+7**	**+7**	**±7**	**±14**	**C1/2 D5 safety labs visit window ±1 days**	
	Adavosertib dispensing and administration													
Adavosertib dispensing		X					X							Section 6.1.1
Adavosertib administration			Dosing on Days 1 to 5 and Days 8 to 12 of 21-day cycle										A minimum of 9 days between the last dosing of a cycle and Day 1 of the next cycle is required.	Section 6.1.1

AE, adverse event; CCI CT, computed tomography; CCI
ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; CCI
MRI, magnetic resonance imaging; CCI ORR, objective response rate; OS, overall survival;
CCI
PK, pharmacokinetics; CCI RECIST v1.1, Response
Evaluation Criteria in Solid Tumors; CCI

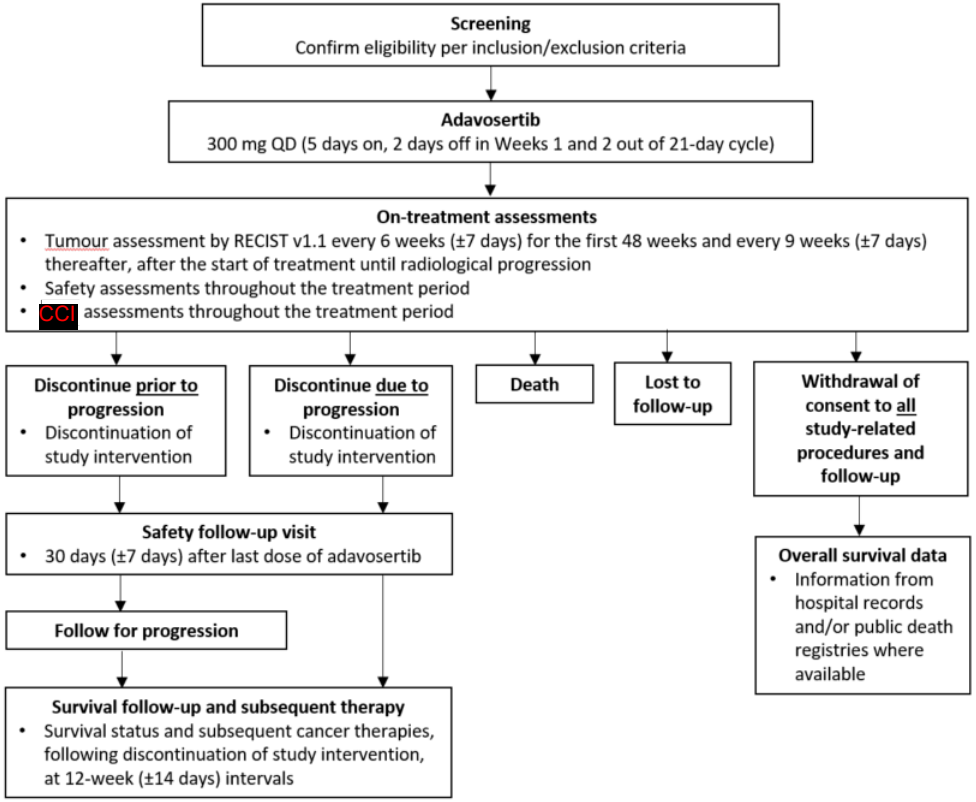
10.2 Appendix B: Study design and flow chart

Figure 1 Study Design



BICR, Blinded Independent Central Review; CT, computed tomography; DCO, data cut-off; ECOG, Eastern Cooperative Oncology Group; FFPE, formalin-fixed paraffin-embedded; HER2, Human epidermal growth factor receptor 2; LPFD, last participant first dose; mo, months; MRI, magnetic resonance imaging; ORR, objective response rate; USC, uterine serous carcinoma; VEGF, vascular endothelial growth factor.

Figure 2 Study Flow Chart



QD, once daily; CCI [redacted] RECIST v1.1, Response Evaluation Criteria in Solid Tumours.

SIGNATURE PAGE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature

Document Name: d601hc00002-sap-ed-2		
Document Title:	Statistical Analysis Plan Edition 2	
Document ID:	Doc ID-004260477	
Version Label:	2.0 CURRENT LATEST APPROVED	
Server Date **(dd-MMM-yyyy HH:mm 'UTC'Z)**	**Signed by**	**Meaning of Signature**
29-Jun-2022 10:41 UTC	PPD	Content Approval
29-Jun-2022 12:13 UTC	PPD	Content Approval
29-Jun-2022 10:12 UTC	PPD PAREXEL	Author Approval

Notes: (1) Document details as stored in ANGEL, an AstraZeneca document management system.