• Protocol number: D5336C00001
• Document title: A Phase II, Open Label, Randomised, Multi-centre Study to Assess the Safety and Efficacy of Agents Targeting DNA Damage Repair in Combination with Olaparib versus Olaparib Monotherapy in the Treatment of Metastatic Triple Negative Breast Cancer Patients Stratified by Alterations in Homologous Recombinant Repair (HRR)-related Genes (including *BRCA1/2*) (VIOLETTE)
• NCT number: NCT03330847
• Version number: 7.0
• Date of the document: 06 May 2020

Clinical Study Protocol	
Drug Substance	Olaparib, AZD1775, Ceralasertib (AZD6738)
Study Code	D5336C00001
Version	7.0 Global
Date	6 May 2020

A Phase II, Open Label, Randomised, Multi-centre Study to Assess the Safety and Efficacy of Agents Targeting DNA Damage Repair in Combination with Olaparib versus Olaparib Monotherapy in the Treatment of Metastatic Triple Negative Breast Cancer Patients Stratified by Alterations in Homologous Recombinant Repair (HRR)-related Genes (including *BRCA1/2*) (VIOLETTE)

Sponsor: *AstraZeneca AB, 151 85 Södertälje, Sweden*

VERSION HISTORY

Version 1.0, 26 Jul 2017
Initial creation

Version 2.0, 18 Sep 2017
Updates based on FDA Comments: - Phenotypic Tumour Selection updated to: Patients should have TNBC (defined as estrogen receptor [ER] and progesterone receptor [PgR] negative [immunohistochemistry [IHC] nuclear staining <1% positive] and human epidermal growth factor receptor 2 [HER2] negative [IHC 0, 1+ or IHC 2+ with corresponding ISH non-amplified of ratio less than 2.0 or ISH non-amplified ratio less than 2.0] as per ASCO-CAP HER2 guideline recommendations 2013 - Section 1.4 and Figure 3 – Updated to include platinum stratification factor for consistency - Inclusion criterion 4 updated to: Histologically or cytologically confirmed TNBC with evidence of metastatic disease (defined as ER and PgR negative [IHC nuclear staining <1% positive] and HER2 negative [IHC 0, 1+ or IHC 2+ with corresponding ISH non-amplified of ratio less than 2.0 or ISH non-amplified ratio less than 2.0] as per ASCO-CAP HER2 guideline recommendations 2013. - Inclusion criterion 8f removed - Section 5.1.1 – updated to include "and irrespective of treatment decisions to clarify the post 72 week RECIST schedule - Section 6.8.2 - following text inserted: Acute toxicities in all treatment arms should be managed as medically indicated, with temporary suspension of IP and initiation of supportive care as clinically indicated by the treating physician. Treatment must be interrupted if any NCI-CTCAE Grade 3 or 4 non-hematologic AE occurs which the Investigator considers to be related to the administration of the study treatment(s). Treatment should not be restarted until the toxicity has resolved to Grade ≤ 1. Repeat dose interruptions are permitted, for a maximum of one cycle of treatment. Any patient who develops a Grade 3 or 4 non-hematologic toxicity that

does not resolve to ≤ Grade 1 within this period, should be removed from the study treatment unless approved by the Medical Monitor

- Synopsis and Section 8.5.1 – Updated to define Cox Proportional Hazard Model.

Administrative Updates:

- Study Title Updated to include VIOLETTE
- Abbreviations updated to include PBMC
- Study Synopsis – Removed reference to "de novo" biopsy and clarified wording
- Study Synopsis – Dosage and Mode of Administration updated to clarify 200mg bd olaparib for AZD1775+olaparib arm
- Table 1 – Footnote updated to remove reference to "de novo" biopsy
- Table 1 – IC#7 added so that patients with non-measurable disease are not screened
- Table 2 and Section 5.2.1.1 – Clarified wording to specify sequential testing for coagulation
- Table 3 – Removed requirement for haematology/chemistry sample at Survival Visit as this was incorrect
- Table 3 and 4 – Footnote j updated as biopsy is not mandatory
- Table 4 – Added footnote l to AZD1775 dose row as this was missing
- Section 1.2.1 typo updated from NSG to NGS
- Figure 3 – Typo corrected to read +/-1 week
- Section 3.2 – Criterion #9 Repetition of QTC interval requirement removed
- Section 5.2.3.1 – Clarified D10 for AZD1775 dose
- Section 5.7 – Specified that biomarker sample to be taken at Screening Part 2
- Section 5.6.1 and Table 2 – Updated text to clarify that genetic sample can be taken at screening or after randomisation
- Section 6.1.1 – Updated typo (Adverse Events to AEs)
- Section 6.6.2 – Updated text to correct paternal exposure to 6 months to remain consistent with rest of protocol
- Section 6.8.1.4 – Wording rearranged for clarity
- Section 7.2 – Repetition removed and typo corrected
- Appendix D, E, F, G and H – Updated Headers to include correct reference
- Appendix D – Updated typo referring to IMP rather than IP
- Appendix F – Updated to specify timing of RECIST measurements

Additional Updates:

- Study Synopsis and Inclusion #5 – Updated text to clarify treatment setting for taxane and/or anthracycline in neo-adjuvant, adjuvant or metastatic setting

- Section 6.8 – Dose reduction of AZD1775 updated to bd dosing to prevent bd to od dosing error
- Section 7.7 – Updated wording to remain consistent with inclusion/exclusion criteria

Version 3.0, 14 Mar 2018 – NOT SUBMITTED

Protocol updates based on sponsor review:

- Throughout document – AZ DMC changed to URC (Unblinded Review Committee)
- Section 1.4 – Clarification that BRCAm does not need to be tumour
- Section 1.4 – Two-Stage consent section – repetition updated
- Section 1.4 – One-Stage consent section – CLIA certified lab updated for global labs.
- Section 1.4 – Figure 3 flow chart updated to specify D7 rather than D8 (typo)
- Section 3.1 – Inclusion criterion 6 updated to clarify HRR genes for entry
- Section 3.1 – inclusion criteria 3 and 7 updated so they do not need to be fulfilled at Screening Part 1
- Section 3.1 – inclusion criterion 8f updated to allow for alternative CrCl calculation methods
- Section 3.3.1 – Details of Lynparza HRR Assay clarified
- Section 3.6 – updated to clarify unblinded roles
- Section 3.7.1 – grapefruit juice restriction updated to prohibited rather than not recommended.
- Section 4 - Table 3 footnote f updated to remove need for triplicate ECGs for AZD6738+olaparib and olaparib and clarify prior to dosing
- Section 4 - Table 4 footnote f updated to clarify triplicate for all ECGs in AZD1775+olaparib arm and prior to dosing
- Section 4 - Table 4 footnote l updated to clarify only 3 day dosing period not 3-5 day dosing period
- Section 5.1 – updated to specify that all scan modalities to be sent for blinded review
- Section 5.4 – section updated to clarify PK timepoints
- Section 5.2.3.1 – typo updated to correct to Day 7 from Day 8 and specific ECG instructions updated for each treatment arm
- Section 5.6.1 – sampling time updated (Visit 1 or after randomisation) to be consistent with Appendix C
- Section 5.7 – updated to include additional exploratory analysis

- Section 6.8.1.1 and 6.8.1.3 – updated with new haematological management information
- Section 6.8.2.2 – typo corrected to 3 day dosing period from 3-5 day dosing period
- Section 7.2 – updated to clarify AZD1775+olaparib dosing regimen and to clarify missed dosing and vomiting for AZD6738
- Section 7.7 – updated to include additional CYP3A interaction details for AZD6738

Updates based on comments from Dutch EC:

- Section 1.2.2 – Typo corrected to remove "inhibitor" in final sentence of 1st paragraph of AZD1775+olaparib rationale
- Section 8.5.5 – Section updated to specify stopping criteria for interim analysis

Updates based on HC Comments:

- Section 6.8.3 updated to now state: Olaparib, AZD1775 and AZD6738 have not been studied in patients with severe renal impairment (CrCl ≤30 mL/min) or end-stage renal disease; if patients develop severe impairment or end stage disease is it recommended that the study treatment be discontinued.
- Section 6.8.2.1 updated to now state: Following investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, then study treatment can be restarted, if deemed appropriate by the Investigator. If significant pulmonary abnormalities are identified but pneumonitis cannot be confirmed, these need to be discussed with the Study Physician. If pneumonitis is confirmed, the patient should be discontinued from study treatment and treated appropriately.
- Section 6.8.2 updated to remove "unless approved by the medical monitor"
- Section 7.7 updated to include "If the use of any strong or moderate inhibitors of CYP3A4 is considered necessary for the patient's safety and welfare, the investigator must interrupt AZD6738 for the duration of concomitant therapy with the CYP3A4 inhibitor and required washout period (5 half-lives for strong and moderate CYP3A4 inhibitors). If the use of any strong or moderate inducers of CYP3A4 is considered necessary for the patient's safety and welfare, this may diminish the clinical efficacy of AZD6738."
- Section 3.4 updated to state "Where a patient does not meet all the eligibility criteria but is randomised in error, or incorrectly started on treatment, the patient should be withdrawn from the study and offered standard of care treatment or enrolment in another clinical trial, as appropriate. The criterion for withdrawal should be appropriately documented."*

- Section 3.9 updated to state “Incorrectly enrolled or treated patients i.e. the patient does not meet the required inclusion/exclusion criteria for the study.”*

These sections were updated in the sponsor review to accommodate the global regions

Updates based on SIDC comments:

- Section 3.8 updated to include pregnancy as discontinuation criterion (also requested by MHRA)

Updates based on comments from MHRA:

- Section 3.7.2 – Updated to include advice for male patients to preserve semen prior to enrolment should they wish to father children while on AZD1775 or 3 months after stopping AZD1775.

Updates based on ANSM comments:

- Section 6.8 - Amended to update to one permitted dose reduction in olaparib for olaparib+AZD1775 arm and update to dose modification tables for olaparib monotherapy to include AZD6738 advice (Also requested by BfARM)
- Section 3.7.3 – New details on sun exposure added (also requested by MHRA)
- Section 6.8.2.1 – Text updated to confirm that olaparib to be discontinued if pneumonitis is confirmed.
- Section 6.8.2 - Table 13 updated to include additional details for QTc interval prolongation dose modification

Version 4.0, 02 May 2018
Protocol updates based on sponsor review: - Synopsis and Sections 1.4, 3 (Inclusion criterion 6), 4 and 8.5 – Updated text to allow for randomisation based on local test results of qualifying HRRm. - Section 3.7.2 – Updated to suggest all male patients to store sperm rather than just those on AZD1775 Administrative Changes: - Table 8 updated for formatting - Exclusion criterion 10 updated to replace typographical error - Table 4 – bd removed from ondansetron and graniestron as not appropriate for this study - Section 6.8.2.2 – reference to bd for ondansetron and granisetron removed for accuracy and reference to patients on qd dosing for AZD1775 removed due to irrelevance

Version 5.0, 03 Jul 2018

Urgent Safety Updates:
 	
- Additional safety Haematology and Clinical chemistry assessment on Cycle 1 Day 8 and Cycle 2 Day 8 and 15 for AZD1775+olaparib treatment arm
- Clarification in Table 4 to perform unscheduled Day 8 and Day 15 complete blood counts in C3 onwards if Grade 3/4 neutropenia, G4 thrombocytopenia or a dose interruption due to haematological toxicity was experienced in a prior cycle.
- Reduction of starting dose of AZD1775 to 150mg BID Days 1-3 and Days 8-10.
- Updated management of IP related toxicities , Dose reductions in Section 6.8 to reflect:
  - Lower starting dose of AZD1775 150mg BID
  - Additional Day 8 and Day 15 visits
  - Change to only 1 dose reduction of AZD1775 permitted
  - Elevated platelet count dosing threshold to platelets $\geq$ 100,000/ μL.
 	
- Section 8.5 updated to include sensitivity analysis

- Updated Section 1.2.2 to provide rationale for 150mg AZD1775 does

Administrative Amendments:

- Table 5 updated to include CCI collection on CXD1 of AZD1775+olaparib in line with other treatment arms
- Table 3 footnote i updated to correspond to original 5.6 text
- Clarity of interpretation provided for exclusion criterion 10
- Table 4 and 5 updated to include CCI on C1D1 as per text in 5.3.1.2
- Section 6.3.1 – Clarity provided on timing of AE and SAE reporting

Updates based on request from Netherlands CEC:

- Section 10.1 – included "latest version" for Declaration of Helsinki, for clarity
- Section 5.1.1 – Anonymised changed to coded for CT scans

Version 6.0, 29 April 2019

Urgent safety issue – AZD1775+olaparib arm closed to recruitment following the Independent Safety Review Committee Meeting 17 April 2019

Protocol synopsis

- Patient numbers randomised adjusted to reflect the reduction following the closure of recruitment in the AZD1775+olaprib arm.
- Total number of sites participating updated to reflect the current status
- Protocol synopsis updated to reflect the recommendation of the Independent Safety Review Committee to close recruitment to the AZD1775+olaparib arm and offer patients the option to continue on olaparib monotherapy 300 mg BID.
- Study period adjusted
- Olaparib+AZD1775 updated to "Olaparib + AZD1775 - this treatment arm was closed following the ISRC meeting on the 17 April 2019"
- Investigational product dosage and mode of administration - updated to reflect the recommendation of the Independent Safety Review Committee to offer patients the option to continue on olaparib monotherapy 300 mg BID on a 21-day cycle.
- AZD1775 supply updated "Following closure of the AZD1775+olaparib arm in April 2019, AZD1775 will no longer be supplied to sites"
- Updated to reflect that following the closure of the AZD1775+olaparib arm in April 2019 patients will either receive olaparib monotherapy and olaparib+AZD6738.

- Statistical section – number of events for the interim and PFS analysis updated following the closure of recruitment to the AZD1775+olaparib arm

Section 1.2.2 and 1.3.2 Title updated to include "Treatment arm closed April 2019"

Sections 1.2.2, 1.3.2, 1.4 Updated to include "Following the ISRC meeting on 17 April 2019 a recommendation was made to close the AZD1775+olaparib treatment arm across all biomarker strata due to increased toxicity and no suggestion of benefit and that patients currently receiving treatment with AZD1775+olaparib treatment be offered the opportunity to continue treatment with olaparib monotherapy at the approved dose (300 mg bd). This recommendation was ratified by the AstraZeneca Unblinded Review Committee and implemented in protocol version 6.0.

Section 1.4

- Sentence added "All patients randomized to this arm discontinued AZD1775 and continued on olaparib monotherapy increasing to the approved dose at the start of their next treatment cycle ensuring a minimum 10 day wash out period from AZD1775 to olaparib 300 mg bd dosing to avoid DDI."
- Treatment Arm 3, sentence added "This treatment arm was closed following the ISRC meeting on the 17 April 2019"
- Sentence added "Following the closure of the olaparib+AZD1775 arm in April 2019 the total number of patients randomised will be lower (approximately 350 patients)."
- Sentence added for clarification, "Due to the closure of the olaparib+AZD1775 arm, fewer than 50 patient per stratum had been randomised to this arm."
- Figure 2 Study Flow Chart updated: Box added "AZD1775+Olaparib CLOSED to new recruitment April 2019" Treatment Arm 3 box updated "**FROM APRIL 2019** 300mg BD Olaparib continuous (21 day cycle)"
- Page 48, Figure 3 Olaparib+AZD1775 boxed crossed through, footnote added "The AZD1775+olaparib treatment arm was closed following the ISRC meeting on the 17 April 2019"

Section 3.5 Sentence added, "AZD1775+olaparib arm was closed in April 2019 so randomisation ratio will be 1:1 to olaparib monotherapy or AZD6738+olaparib."

Section 3.6 Sentence updated "Given the study treatment design (monotherapy and 2 different combination therapies will be employed; **monotherapy and 1 combination from April 2019**) neither patients nor Investigators will be blinded to study treatment.

Section 3.8.1 Sentence added, "Following the ISRC meeting on 17 April 2019 a recommendation was made to close the AZD1775+olaparib treatment arm across all biomarker strata and that patients currently receiving treatment with AZD1775+olaparib treatment be offered the opportunity to continue treatment of olaparib monotherapy at the approved dose (300 mg bd) at the next treatment cycle."

Section 4.

- Sentence added following the ISRC meeting. "Patients on treatment in April 2019 when the AZD1775+olaparib arm was closed will be offered the opportunity to continue treatment of olaparib monotherapy at the approved dose (300 mg bd) at their next treatment cycle and should follow Table 5 continuing treatment on a 21-day cycle.
- Table 5 olaparib +AZD1775 Schedule of Assessments
    - Title updated to include "(applies to Patients Randomised to this Treatment Arm who, after April 2019, continue on olaparib monotherapy)".
    - Blood sample required for [redacted] analysis in cycle 2.
    - Pharmacogenetic sample and footnote added
    - Footnote f updated to confirm that from April 2019 triplicate ECG no longer applies to patients who have discontinued AZD1775 but single ECGs should be taken at the stated timepoint.
    - Footnote k updated to confirm that PK time windows are no longer applicable following CSPv6.0
    - Footnote l updated to confirm that aprepitant and fosaprepitant are permitted following a washout period "No longer applicable following CSPV6.0, provided there has been a minimum washout period of 10 days since the final dose of AZD1775 of 10 days**"**
    - Footnote m updated to clarify that a sample is required either at the scan visit or the CxD1 visit not both if the two visits do not coincide
    - Footnote o updated to clarify that unscheduled blood counts are no longer applicable following CSPv6.0
    - Footnote ** updated to add a sentence "After April 2019, all patients randomised to this treatment arm discontinued AZD1775 and were offered the opportunity to continue olaparib monotherapy at 300 mg bd on a 21-day cycle starting at the patient's next treatment cycle to ensure a minimum 10 day wash out period from AZD1775 to olaparib monotherapy 300 mg bd dosing to avoid DDI."

Section 5.2.3.1 "A single ECG is required at subsequent timepoints for patients in the olaparib monotherapy or AZD6738+olaparib arms, and triplicate ECGs for patients in the AZD1775+olaparib treatment arm **(from April 2019 triplicate ECG no longer applies to patients who have discontinued AZD1775 but single ECGs should be taken at the stated timepoints).**

Section 5.4 Pharmacokinetics, "AZD1775 and olaparib arm – **this treatment arm was closed following the ISRC meeting on 17 April 2019"**

Section 6.8

- Page 108 Updated sentence added. "***No longer applies from CSPv6.*** For AZD1775, only 1 dose reduction will be allowed. Patients requiring >1 dose reduction will be discontinued from the study drug. Only one dose reduction in olaparib is permitted in the AZD1775+olaparib treatment arm."
- Table 9 title updated "**No longer applies from CSPv6.0** - AZD1775+olaparib dose reduction"
- Page 108, additional wording added - Due to the recommendation to close the AZD1775+olaparib arm in April 2019 patients continuing treatment on the AZD1775+olaparib treatment arm should be offered the opportunity to escalate the dose of olaparib to 300 mg bd continuing on a 21-day cycle starting at the patient's next treatment cycle. If a patient has had a dose reduction due to toxicity on this treatment combination, the investigator may consider a stepwise increment in the olaparib dose at their discretion, e.g. 200 mg, 250 mg then 300 mg. The visit schedule should be followed as per Table 5 at escalation**.** For patients continuing on olaparib monotherapy at 300 mg bd please follow the toxicity management guidance as per olaparib monotherapy.

Section 6.8.1.1 and 6.8.1.2 title, additional information added (includes patients continuing on olaparib monotherapy randomised to the AZD1775+olaparib arm)

Table 13 updated for clarity, CTCAE Grade 1-2 (Investigator judgement **whether** to continue treatment **or** dose interrupt**.** CCI [redacted]

Section 6.8.1.3 "**Not applicable following CSPv6.0"**

Section 6.8.2, 6.8.2.2 updated to AZD1775 – **this treatment arm was closed following the ISRC meeting on 17 April 2019.**

Section 6.8.2 Table 17 header updated to include "no longer applicable following CSPv6.0).

Section 6.8.2.2 Please note: aprepitant (Emend) and fosaprepitant are not permitted due to known DDIs. N**o longer applicable following CSPV6.0, provided there has been a minimum washout period of 10 days since the final dose of AZD1775.**

Section 7

- Section 7.1 updated, "AstraZeneca's Pharmaceutical Development, R&D Supply Chain will supply olaparib, AZD6738 and AZD1775 to the Investigators. **Following the ISRC meeting on 17 April 2019 and the recommendation to close the AZD1775+olaparib treatment arm across all biomarker strata AZD1775 will not be supplied to sites.** Summary table updated "AZD1775 (not applicable from CSPv6.0)"
- Section 7.2 added "Following the ISRC meeting on 17 April 2019 a recommendation was made to close the AZD1775+olaparib treatment arm across all

biomarker strata and that patients currently receiving treatment with AZD177+olaparib treatment be offered the opportunity to continue treatment of olaparib monotherapy at the approved dose 300 mg bd at the patient's next treatment cycle."

- Section 7.7, AZD1775 added "**Not applicable following CSPv6.0**" and aprepitant (Emend) and fosaprepitant are not permitted due to known DDIs. N**o longer applicable following CSPV6.0, provided there has been a minimum washout period of 10 days since the final dose of AZD1775.**

Section 8

Section 8.1 and 8.5.5 PFS events updated to reflect the closure of the AZD1775+olaparib treatment arm.
Section 8.2

- Sentence added "Following the decision of the ISRC to close recruitment to the AZD1775 + olaparib arm, the study will only be sized to detect a difference for the AZD6738 + olaparib vs olaparib monotherapy comparison"
- Text removed "Overall, 102 PFS events are required in each biomarker stratum (306 across all strata)".
- Text added, Following the closure of the olaparib+AZD1775 arm in April 2019, fewer than 50 patient per strata will be randomised to this arm and the total number of patients randomised will be lower (approximately 350 patients).
- Section 8.5, page 128, text added "Following the decision of the ISRC to close recruitment to the AZD1775 + olaparib arm, the study will only be sized to detect a difference for the AZD6738 + olaparib vs olaparib monotherapy comparison, although all the available data across all 3 arms, where possible, will be used in the statistical models.

Appendix H Added, Not applicable following CSPv6.0 provided there has been a minimum washout period of 10 days since the final dose of AZD1775:

Study Team updates

Section 1.4 Page 52, enrolment updated to randomisation

Sections 3.1 and 3.2:

- Inclusion criterion 4 updated for clarification: * Histologically or cytologically confirmed TNBC **at initial diagnosis** with evidence of metastatic **or incurable advanced locoregional disease** (defined as ER and PgR negative [IHC nuclear staining <1% positive] and HER2 negative [IHC 0, 1+ or IHC 2+ with corresponding ISH non-amplified of ratio less than 2.0 or ISH non-amplified ratio less than 2.0] as per ASCO-CAP HER2 guideline recommendations 2013 (ASCO-CAP). **Note: An Allred score of 0-2 is acceptable however for a score of 2 the**

Proportion score must be checked to make sure it is 1 (≤1% cells are ER positive).

- Inclusion criterion 5 updated for clarification: * Patients must have received at least 1 and no more than 2 prior lines of treatment for metastatic **or incurable advanced locoregional disease** with an anthracycline (eg, doxorubicin, epirubicin) and/or a taxane (eg, paclitaxel, docetaxel) unless contraindicated, in either the neo-adjuvant, adjuvant or metastatic setting.
- Exclusion criterion 9 updated for clarification: ***No longer applicable from CSPv6.0*** AZD1775 should not be given to patients who have a history of Torsades de pointes unless all risk factors that contributed to Torsades have been corrected. AZD1775 has not been studied in patients with ventricular arrhythmias or recent myocardial infarction.

Section 4, Table 2 updated for consistency, inclusion criteria 3 and 7 and exclusion criterion 14 are not required for screening part 1, inclusion criterion 8 is required for screening part 1. Footnote b updated to change enrolment to randomisation.

Table 3, pharmacogenetic sample removed and added to Tables 4 and 5.

Section 4.1, page 77 enrolled updated to randomised in the study

Section 5.2.3.1, Update to the supine body position from 30 to 45 degree flexion, "The patients will rest for at least 10 minutes before the start of each recording and they must be in the same supine body position (**45** degree flexion in the hip and feet not in contact with the footboard) at the recording time point."

Section 6.1.8.2 Sentence added, G-CSF should not be used within 24hrs of the last dose prior to dose interruption.

Section 9.3 Updated to reflect start date of Q1 2018

Appendix D Updated to reflect current Hy's Law language

Appendix E Correction from 3 to 6 months abstinence after the last dose for male patients

Investigator brochure updates

Section 1.3.1 Dyspnoea added as an adverse drug reaction for olaparib.

Section 1.3.2 Page 42, febrile neutropenia added as an adverse drug reaction for AZD1775. Sentence added to refer to the AZD1775 IB for information on the assessment of potential and known risk.

Version 7.0, 6 May 2020

AZD6738 updated to ceralasertib throughout

Clinical Study Protocol and Synopsis study period extended to Q4 2020

Section 1.3.1: US indication updated to current

Section 1.4: Stage 1 consent clarification, update to Figure 2 to incorporate language for data collection following the data cut off for the final PFS analysis per stratum

Section 3.2: Exclusion criterion 11 – updated to clarify which exclusions apply following the closure of the 1775 treatment arm in April 2019

Section 3.8.1: Duration of the survival follow up clarified

Section 4: Table 4 and Table 5

- Guidance on data collection following the final analysis for PFS for each stratum
- Table 5 Footnote added to describe the additional clinical chemistry and hematology assessments on Day 8 and Day 15 required following grade 3 or grade 4 thrombocytopenia or neutropenia in a previous cycle.
- Medication accountability added, section 7.2 updated

Section 4: Table 6 added: Summary of data entry required and sample collection following the final analysis for PFS for each stratum

Section 5.1.2: Clarification that scans will only be sent to the Central Imaging Vendor up until the final analysis for the PFS.

Section 5.2: Guidance provided on data collection in all sub sections for patients continuing on treatment following the final analysis for PFS in each stratum.

Section 5.3.1.2: Following the final analysis for PFS for each stratum patient CCI [redacted] CCI is not required

Section 5.7: Clarification that patients with a previous confirmed quality mutation at screening will have their samples shipped for central assessment afterrandomisation. Following the final analysis for PFS for each stratum exploratory blood samples are not required with the exception of a blood sample for CCI [redacted] analysis at the time of disease progression

Section 6.3.1.1: Updated wording for adverse events after the 30-day follow-up period

Section 6.4: Regulatory Reporting Requirements for SAEs added.

Section 6.8.1.1 and 6.8.1.2:

- Text updated to align with the protocol clarification memo for management of haematological toxicity (dated 26 September 2019, protocol version 6.0).
- Additional guidance for haematological toxicity inserted.
- Table 13 dose modification language clarified

Section 7.2: Text updated for medication accountability at each cycle.

Section 7.7.1: Guidance provided on concomitant medication data collection for patients continuing on treatment following the final analysis for PFS in each stratum.

Section 9.2.1: Text updated for documentation of source data.

Section 9.3: Guidance for data collection following the data cut off for the final analysis for the PFS for each stratum for patients remaining on treatment or in survival follow up

Section 9.4: Text updated for data management.

Section 10.1, 10.2: Updates to the text for the Ethical Conduct of the Study. Subsections 10.4, 10.8 and 10.9 Financial Disclosure, Study and Site Closure and Dissemination of Clinical Study Data added.

Appendix D: Updates to the Hy's Law language

Updated based on FAMHP comments:

- Section 7.7 Language added about coadministration of drugs that are either completely metabolized by CYP2C8 or that are substrates of CYP2C8 and also have a narrow therapeutic index to align with the current ceralasertib IB
- Appendix I ceralasertib guidelines for potential interactions with concomitant medications added

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

CLINICAL STUDY PROTOCOL SYNOPSIS

A Phase II, Open Label, Randomised, Multi-centre Study to Assess the Safety and Efficacy of Agents Targeting DNA Damage Repair in Combination with Olaparib versus Olaparib Monotherapy in the Treatment of Metastatic Triple Negative Breast Cancer Patients Stratified by Alterations in Homologous Recombinant Repair (HRR)-related Genes (including *BRCA1/2*) (VIOLETTE)

International Co-ordinating Investigator

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Study site(s) and number of patients planned

The study will be conducted globally and approximately 450 patients will be randomised to the study. Following the closure of the olaparib+AZD1775 arm in April 2019, the total number of patients randomised will be lower (approximately 350 patients).

It is planned to initiate 172 sites, each recruiting 3 to 4 patients.

The study will aim to randomise a total of approximately 450 patients; approximately 50 patients for each of the 3 study treatment arms in each of the 3 biomarker strata.

Following the ISRC meeting on 17 April 2019 a recommendation was made to close the AZD1775+olaparib treatment arm across all biomarker strata and that patients currently receiving treatment with AZD1775+olaparib treatment be offered the opportunity to continue treatment on olaparib monotherapy at the approved dose (300 mg bd). Following the closure of this arm the total number of patients randomised will be lower (approximately 350 patients).

This recommendation was ratified by the AstraZeneca Unblinded Review Committee and implemented in Clinical Study Protocol Version 6.0 (CSPv6.0)

Phase of development 2

Study period		Phase of development
Date of first patient enrolled	Q1 2018	2
Estimated date of last patient completed	Q4 2020	2

Study design

This is a prospective, open label, randomised, multi-centre Phase 2 study that will assess the safety and efficacy of olaparib monotherapy versus olaparib in combination with an inhibitor of Ataxia Telangiectasia and Rad3-related protein (*ATR*) (ceralasertib) and olaparib monotherapy versus olaparib in combination with an inhibitor of WEE1 (AZD1775) in second or third line setting in patients with Triple Negative Breast Cancer (TNBC) stratified by qualifying tumour mutation(s) in any of CCI genes involved in the Homologous Recombination Repair (HRR) pathway.

There will be 3 treatment arms (approximately 150 patients in each treatment arm):

- Olaparib + AZD1775 – **this treatment arm was closed following the ISRC meeting on the 17 April 2019**
- Olaparib + ceralasertib
- Olaparib

Objectives

Study objectives are defined for the following patient populations:

- "Breast cancer susceptible gene mutation (*BRCAm*)" = patients from stratum A
- "Homologous Recombination Repair gene mutation (HRR*m*)" = patients from stratum A and patients from stratum B
- "Non *BRCAm* HRR*m*" = patients from stratum B
- "All" = patients from any stratum
- "Non HRR*m*" = patients from stratum C

Patient Population	Primary Objective	Outcome Measure
• *BRCAm* • Non *BRCAm* HRR*m* • Non HRR*m*	To assess the efficacy of the combination of ceralasertib+olaparib and the combination of AZD1775+olaparib compared with olaparib monotherapy by assessment of progression free survival (PFS)	PFS using Blinded Independent Central Review (BICR) according to Response Evaluation Criteria in Solid Tumours (RECIST 1.1) Sensitivity analysis of PFS using Investigator assessments according to RECIST 1.1

Patient Population	Secondary Objectives	Outcome Measures
• HRR*m* • All	To assess the efficacy of the combination of AZD6738+olaparib and the combination of AZD1775+olaparib compared with olaparib monotherapy by assessment of PFS	PFS using Blinded Independent Central Review (BICR) according to Response Evaluation Criteria in Solid Tumours (RECIST 1.1) Sensitivity analysis of PFS using Investigator assessments according to RECIST 1.1
• *BRCAm* • HRR*m* • Non *BRCAm* HRR*m* • All • Non HRR*m*	To assess the efficacy of the combination of AZD6738+olaparib and the combination of AZD1775+olaparib compared with olaparib monotherapy in terms of • objective response rate (ORR)	Objective response using BICR according to RECIST 1.1 Sensitivity analysis of objective response using Investigator assessments according to RECIST 1.1
• *BRCAm* • Non *BRCAm* HRR*m* • Non HRR*m*	To assess the efficacy of the combination of AZD6738+olaparib and the combination of AZD1775+olaparib compared with olaparib monotherapy in terms of • duration of response (DoR) • tumour change	DoR and tumour change using BICR according to RECIST 1.1 Sensitivity analysis of DoR, and tumour change using Investigator assessments according to RECIST 1.1
• *BRCAm* • HRR*m* • Non *BRCAm* HRR*m* • All • Non HRR*m*	To assess the efficacy of the combination of AZD6738+olaparib and the combination of AZD1775+olaparib compared with olaparib monotherapy in terms of overall survival (OS)	Time to death for any cause

Patient Population	Secondary Objectives	Outcome Measures
• *BRCAm* • HRR*m* • Non *BRCAm* HRR*m* • All • Non HRR*m*	To compare the efficacy of the combination of AZD6738+olaparib with the combination of AZD1775+olaparib in terms of • PFS • ORR	PFS and objective response using BICR according to RECIST 1.1 Sensitivity analysis of PFS and objective response using Investigator assessments according to RECIST 1.1
• *BRCAm* • Non *BRCAm* HRR*m* • Non HRR*m*	To compare the efficacy of the combination of AZD6738+olaparib with the combination of AZD1775+olaparib in terms of • DoR • tumour change	DoR and tumour change using BICR according to RECIST 1.1 Sensitivity analysis of DoR and tumour change using Investigator assessments according to RECIST 1.1
• *BRCAm* • HRR*m* • Non *BRCAm* HRR*m* • All • Non HRR*m*	To compare the efficacy of the combination of AZD6738+olaparib with the combination of AZD1775+olaparib in terms of OS	Time to death for any cause
• All	To explore the frequency of and describe the nature of tumour HRR (including *BRCA*) mutation(s) in tumour samples and to compare this with germline HRR (including *BRCA*) mutation status	Mutation status of CCI genes
• All	To assess exposure to olaparib, AZD6738 and AZD1775 in all patients	Minimum concentration at steady state ($C_{min\ ss}$)

Patient Population	Secondary Objectives	Outcome Measures
Patient Population	**Safety Objective**	**Outcome Measure**
• All	To assess the safety and tolerability of the combination of ceralasertib+olaparib and the combination of AZD1775+olaparib compared with olaparib monotherapy	• Adverse events (AEs) (severity graded by Common Terminology Criteria for Adverse Event [CTCAE] v4) • laboratory tests (clinical chemistry, haematology and urinalysis) • vital signs (pulse and blood pressure [BP]) • electrocardiogram (ECG) data • Eastern Cooperative Oncology Group performance status (ECOG PS) (see Appendix F)

Patient Population	Exploratory Objectives	Outcome Measure
• All	CCI	CCI
• *BRCAm* • HRR*m* • Non *BRCAm* HRR*m* • All • Non HRR*m*	CCI	CCI

Patient Population	Exploratory Objectives	Outcome Measure
• All	CCI	CCI
• All	CCI	CCI

Target patient population

All patients randomised in the study will be selected based on the following 3 principles in order of decreasing priority:

Biomarker selection

– Patients with documented presence or absence of qualifying mutation(s) in tumour tissue predicted to be deleterious or suspected deleterious in one of CCI HRR genes. All patients must provide a formalin-fixed paraffin embedded (FFPE) tumour specimen sample for tissue-based HRR gene panel testing using the clinical trial assay (CTA) known as the Lynparza HRR assay. Tumour tissue samples can be obtained/can originate from either primary tumour (eg, archival breast cancer specimen) or metastatic biopsy. If an archival FFPE sample from the primary tumour is not available for molecular analysis, an FFPE sample from a biopsy of a metastatic lesion, collected following progression on a prior line of therapy, may be used for this testing. The tumour sample will be tested for mutation in CCI pre-specified HRR genes. If the test results indicate that the

patient has a qualifying mutation in the breast cancer susceptible genes 1 or 2 (*BRCA1* or *BRCA2)*, the patient is eligible for stratum A of the study. If the results indicate that the patient has a qualifying mutation in any of the remaining[CCI] HRR genes [CCI] and does not have a qualifying mutation in either *BRCA1* or *BRCA2* genes, the patient is eligible for stratum B. If the results indicate that the patient has no detected qualifying mutation in any of the [CCI] HRR genes, the patient is eligible for stratum C. Prospective screening will be implemented to ensure equal patient numbers in each stratum (*BRCAm*, non *BRCA* HRR*m*, and non HRR*m*). Foundation Medicine, Inc. (FMI) will provide the CTA, a novel next generation sequencing (NGS)-based assay, that will be performed as a single laboratory testing service using DNA extracted from FFPE tissue. Patients may be randomised based on a local test verified and validated in line with local regulations, within a GCP laboratory showing a qualifying mutation in any of the [CCI] HRR genes but must provide sufficient tissue sample for retrospective analysis with the FMI test.

Treatment setting

- No less than 1 and no more than 2 prior lines of cytotoxic chemotherapy for metastatic disease are allowed which means that, to be eligible, patients should be suitable for chemotherapy in either a second or third line setting. All patients must have received treatment with an anthracycline and/or taxane unless contraindicated, in the either the neo-adjuvant, adjuvant or metastatic setting. Prior therapy with platinum for metastatic breast cancer is allowed provided there has been no evidence of disease progression during platinum treatment. In addition, patients may have received prior platinum as potentially curative treatment for a prior non breast cancer (eg, ovarian cancer) with no evidence of disease for ≥ 5 years prior to study entry or as adjuvant/neoadjuvant treatment for breast cancer provided at least 12 months have elapsed between the last dose of platinum-based treatment and randomisation. Patients should not have previously received a polyadenosine 5'diphosphoribose (PARP) inhibitor or DNA damage response/repair (DDR) inhibitors (unless treatment was for less than 3 weeks duration and at least 12 months have elapsed between the last dose and randomisation. Patients that did not tolerate prior treatment are excluded).

Phenotypic tumour selection

- Patients should have TNBC (defined as estrogen receptor [ER] and progesterone receptor [PgR] negative [immunohistochemistry [IHC] nuclear staining <1% positive] and human epidermal growth factor

receptor 2 [HER2] negative [IHC 0, 1+ or IHC 2+ with corresponding ISH non-amplified of ratio less than 2.0 or ISH non-amplified ratio less than 2.0] as per ASCO-CAP HER2 guideline recommendations 2013 (ASCO-CAP).

Duration of treatment

Patients should continue to receive study treatment until objective radiological disease progression as per RECIST 1.1 as assessed by the Investigator or unacceptable toxicity occurs and they do not meet any other discontinuation criteria. Once patients have been discontinued from study treatment, other treatment options will be at the discretion of the Investigator.

All patients should continue RECIST 1.1 assessments until documented evidence of objective radiological progression in accordance with RECIST 1.1, irrespective of treatment decisions (ie, RECIST 1.1 follow up until progression even if a patient discontinues study treatment prior to progression and/or receives a subsequent therapy prior to progression).

Investigational product (IP), dosage and mode of administration

Olaparib and ceralasertib will be provided to patients participating in this study in a 28-day cycle. Those on the AZD1775+olaparib arm will be on a 21-day cycle.

- Olaparib will be supplied as 150 mg or 100 mg film coated tablets. Patients will be administered olaparib orally twice daily (bd) at 300 mg on the olaparib monotherapy and ceralasertib+olaparib arms and 200mg bd on the AZD1775+olaparib arm. Following closure of the AZD1775+olaparib arm in April 2019 patients receiving active treatment will be offered the opportunity to continue treatment with olaparib monotherapy at the approved dose twice daily (bd) at 300mg at the patient's next cycle on a 21-day cycle. Patients that have experienced toxicities on the AZD1775+olaparib arm resulting in olaparib being dose reduced will have the option to increase the olaparib dose in a stepwise fashion at the discretion of the investigator.

- Ceralasertib will be supplied as 20 mg, 80 mg, or 100 mg film coated tablets. Patients will be administered ceralasertib once daily (od) at 160 mg from D1-D7 (inclusive) of every cycle.

- AZD1775 will be supplied as dry-filled capsules containing 25 mg, 50 mg, 75 mg, 100 mg, or 200 mg of drug substance. Patients will be administered AZD1775 bd at 150 mg on D1-3 and D8-10. Following closure of the AZD1775+olaparib arm in April 2019, AZD1775 will no longer be supplied to sites.

Patients will either receive olaparib alone or olaparib+AZD6738 or olaparib+AZD1775, following the closure of the AZD1775 arm in April 2019, patients will either receive olaparib monotherapy or olaparib+ceralasertib.

Statistical methods

Statistical analyses will be performed by AstraZeneca or its representatives including Contract Research Organisations (CROs). Further details of the statistical analyses will be described in a Statistical Analysis Plan (SAP).

Primary statistical analyses comparing PFS based on BICR for each combination of treatment arms to olaparib will be conducted for the 3 patient populations *BRCAm*, non *BRCAm* HRR*m* and non HRR*m*.

Multiplicity adjustment will be considered within each of the 3 primary patient populations for PFS. The overall alpha for each primary patient population will be 0.2, and a simple Bonferroni adjustment assigns an alpha of 0.1 to each of the 2 pairwise treatment arm comparisons to olaparib. No further adjustments for multiplicity are planned.

For the non HRR*m* population an interim futility analysis will be triggered when 75 patients have been recruited and assessed for at least 8 weeks, in order to assess the proportion of patients with Non Progressive Disease (NPD), based on the Investigator assessment at 8 weeks in each of the treatment arms. Recruitment will be paused after the 75th patient has been recruited into this population, until the AZ URC confirms which treatment arms should be reopened.

A further NPD futility interim analysis in the non *BRCAm* HRR*m* population may be performed, if the outcome of the interim analysis in the non HRR*m* population resulted in treatment arms being stopped.

For each of the 3 primary patient populations

- an interim analysis for PFS is triggered when 44 PFS events for the ceralasertib+olaparib vs olaparib monotherapy pairwise comparison in that particular patient population have occurred (as the non HRR*m* patient population is expected to be enrolled quicker than the other patient populations, it is expected that the interim analysis for this patient population will occur first, followed by interim analyses for the 2 other primary patient populations)

- the final analysis for PFS is triggered when 68 PFS events for the ceralasertib+olaparib vs olaparib monotherapy pairwise comparison in that particular patient population have occurred (final analyses may be concurrent or separate depending on the recruitment and PFS event rates and other optional requirements)

- PFS will be analysed using pair-wise log rank tests (using the Breslow approach for handling ties) stratified by prior platinum-based therapy for generation of the p-value; pair-wise hazard ratios (HRs) and two-sided 90% confidence intervals (CIs) will be estimated from a stratified Cox Proportional Hazards model (with ties = Efron) with a prior platinum-based therapy (Y/N) term included in the strata statement and the CIs calculated using a profile likelihood approach.

- a Kaplan-Meier (KM) plot of PFS will be presented by treatment group (overall and stratified by prior platinum-based therapy)

- for each of the pair-wise treatment arm comparisons, 68 PFS events would have 80% power to show a statistically significant difference at the two-sided 10% significance level if the assumed true treatment effects were HR 0.55; this relates to

  – a 5-month benefit in median PFS over 6 months on olaparib in the *BRCAm* population

  – a 4.17-month benefit in median PFS over 5 months on olaparib in the non *BRCAm* HRR*m* patient population and in the non HRR*m* patient population

  if PFS is exponentially distributed

- approximately 50 patients will be randomised to each of the 3 treatment arms within each of the 3 biomarker strata so that data maturity for the PFS analysis is approximately 68%. Following the closure of the olaparib+AZD1775 arm in April 2019, fewer than 50 patient per strata will be randomised to this arm.

- an initial OS analysis will be performed at the same time as the primary analysis of PFS; a further analysis of OS will be performed when the OS data are approximately 70% mature .

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse Event of Special Interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AML	Acute myeloid leukaemia
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
ATM	Ataxia Telangiectasia mutated
ATR	Ataxia Telangiectasia and Rad3-related protein
AZ	AstraZeneca
BCRP	Breast cancer resistance protein
bd	bis in die; twice daily
BICR	Blinded Independent Central Review
BP	Blood pressure
BRCA1 and *BRCA2*	Breast cancer susceptible gene 1 and 2
BRCAm	Breast cancer susceptible gene mutation
BUN	Blood urea nitrogen
CDK	Cyclin-dependent kinases
CI	Confidence interval
CLIA	Clinical Laboratory Improvement Amendments
$C_{min\ ss}$	Minimum concentration at steady state
CNS	Central nervous system
CR	Complete response
CRO	Contract Research Organisation
CrCl	Creatinine clearance
CRF	Case Report Form (electronic/paper)
CSA	Clinical Study Agreement
CSR	Clinical Study Report

Abbreviation or special term	Explanation
CT	Computed tomography
CTA	Clinical trial assay
CTCAE	Common Terminology Criteria for Adverse Event
CCI	CCI
CYP	Cytochrome P
DCIS	Ductal carcinoma *in situ*
DDI	Drug-drug interaction
DDR	DNA damage response/repair
DHEA	Dehydroepiandrosterone
DNA	Deoxyribonucleic acid
DoR	Duration of response
DSB	Double strand break
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group performance status: a performance status using scales and criteria to assess how a patient's disease is progressing
eCRF	Electronic Case Report Form
EDoR	Expected duration of response
CCI	[redacted]
ER	Estrogen receptor
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
FFPE	Formalin fixed paraffin embedded
FMI	Foundation Medicine, Inc.
g*BRCAm*	Germline *BRCA* mutation
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GMP	Good Manufacturing Practice
Hb	Haemoglobin
HER2	Human epidermal growth factor receptor 2

Abbreviation or special term	Explanation
HGSOC	High-grade serous ovarian carcinoma
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRD	Homologous recombination deficiency
HRR	Homologous Recombination Repair
HRR*m*	Homologous Recombination Repair gene mutation
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ID	Identification
IHC	Immunohistochemistry
IMPD	Investigational Medicinal Product Dossier
INR	International normalised ratio
International Co-ordinating Investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the Investigators and/or activities internationally.
IP	Investigational Product
IRT	Interactive Response Technology
ISRC	Independent Safety Review Committee
ITT	Intent to treat
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
KM	Kaplan-Meier
LSLV	Last Subject Last Visit
MCV	Mean cell volume
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
CCI	[redacted]
NCI	National Cancer Institute
NE	Not evaluable
NGS	Next generation sequencing
NPD	Non Progressive Disease

Abbreviation or special term	Explanation
NYHA	New York Heart Association
OAE	Other Significant Adverse Event
od	Once daily
ORR	Objective response rate
OS	Overall survival
PARP	Polyadenosine 5'diphosphoribose (poly [ADP ribose])
PD	Progressive disease
PDx	Pharmacodynamics
PFS	Progression free survival
P-gp	Permeability glycoprotein
PgR	Progesterone receptor
PI	Principal Investigator
PK	Pharmacokinetics
PBMC	Peripheral Blood Mononuclear Cell
PR	Partial response
CCI	[redacted]
qd	quaque die; every day
CCI	[redacted]
RECIST	Response Evaluation Criteria In Solid Tumours
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable disease
SSB	Single strand breaks
TL	Target lesion
TNBC	Triple Negative Breast Cancer
ULN	Upper limit of normal
URC	Unblinded Review Committee
USA	United States of America

1. INTRODUCTION

1.1 Background and rationale for conducting this study

Deoxyribonucleic acid damage and its repair or lack thereof is central to the induction of mutations which drive the development of nearly all cancers. Healthy cells defend themselves against the deleterious effects of DNA damage through an interrelated series of molecular pathways, the DDR that recognizes DNA damage, stalls the cell cycle, and mediates DNA repair, thus maintaining the integrity of the genome. Key to DDR are the PARP1 and PARP2 enzymes. *BRCA1* and *BRCA2* defective tumours are intrinsically sensitive to PARP inhibitors, both in tumour models in vivo (Rottenberg et al 2008, GLOBOCAN 2012, Hay et al 2009) and are the first clinically approved drugs designed to exploit synthetic lethality in patients (Fong et al 2009).

The term "*BRCA*ness" has been used to describe tumours that have not arisen from a *BRCA1* or *BRCA2* mutation but nonetheless share certain phenotypes, in particular HRR gene alterations. Deficiencies in a number of tumour suppressor genes involved in HRR, such as *ATM* and *ATR*, may share the same therapeutic vulnerabilities with *BRCAm* tumours and confer sensitivity to PARP inhibition. Therefore, tumours with HRR mutations may also respond to PARP inhibitor treatment.

The ability of PARP inhibition to sensitise tumour cells to DNA-damaging chemotherapies provided the initial rationale for combining PARP inhibitors with chemotherapy. However, clinical experience has shown mixed results with dose-limiting normal tissue toxicity when combined with the standard dose of the chemotherapy. Supported by preclinical evidence, interest has garnered in combining PARP inhibitors with targeted agents that impair the ability of tumour cells to stall the cell cycle to process and repair trapped PARP1 DNA lesions, eg, WEE1 and *ATR*. This can now be tested in patient subpopulations with molecular alterations of the HRR pathway.

1.1.1 Background and rationale for TNBC

Breast cancer is a life-threatening disease and is the leading cause of cancer death among women. In the European Community, the estimated age adjusted annual incidence in 2012 was 71.1/100 000 and the mortality 16.1/100 000 (GLOBOCAN 2012).

Approximately 5% of breast cancers are associated with alterations in the *BRCA1* and/or *BRCA2* gene with approximately 3% associated with the *BRCA1* gene (generally TNBC), and approximately 2% associated with the *BRCA2* gene (generally hormone receptor positive ER+). In the general population, *BRCA* alteration carriers have an increased relative risk of breast cancer. Presence of *BRCA1* mutations is associated with a 60 to 70% lifetime risk of breast cancer and a 20 to 45% lifetime risk of ovarian cancer (Antoniou et al 2003). Presence of *BRCA2* mutations is associated with a 40 to 60% lifetime risk in women and 5 to 10% in men of breast cancer and a 10 to 20% lifetime risk of ovarian cancer. Rare individuals carry deleterious mutations in both *BRCA1* and *BRCA2* genes.

Although there are phenotypic differences in breast cancers resulting from *BRCA1* or *BRCA2* mutations, their important commonality is that mutations in either gene result in tumours that are deficient in HRR, making both appropriate for treatment with PARP inhibitors whereby the process of synthetic lethality can be exploited. In a previous AstraZeneca (AZ) sponsored Phase II proof of concept study in patients with *BRCA* mutated (*BRCAm*) breast cancer (Study D0810C00008), approximately 60% of patients had *BRCA1* mutations (the other 40% had *BRCA2* mutations) with 55% of tumours with TNBC subtype. In this study, anti-tumour activity was seen in patients with either *BRCA1* or *BRCA2* mutations (Tutt et al 2010).

Given the small size of the *BRCAm* subpopulation in breast cancer, information comparing the outcome from this subpopulation with the overall breast cancer population is based on reports from a number of small studies (Krammer et al 2017, Robson et al 2004, Rennert et al 2007, van den Broek et al 2015), and firm conclusions cannot be drawn. The overall body of evidence suggests that once baseline prognostic factors (such as hormone receptor and HER2 status) and treatment are taken into account, *BRCAm* patients have a similar outcome to their biomarker negative counterparts. This is in contrast to patients with *BRCAm* ovarian cancer who have an improved survival compared with non carriers, particularly if they receive platinum-based therapy. In addition, patients with platinum-sensitive, recurrent ovarian cancer with somatic *BRCA* mutations showed a similar reduction in the risk of disease progression when treated with a PARP inhibitor as those with germline *BRCAm* (Ledermann et al 2014), and, in a separate study, patients with a proposed HRD genomic scar showed extension in PFS relative to biomarker negative patients (Kristeleit et al 2015). However, further studies are warranted to identify distinct patient subpopulations most likely to benefit from PARP inhibition or combination therapy, in *BRCAm* breast cancer patients where there are no approved treatments and patients are treated according to their hormone receptor and HER2 status.

Mutations in *BRCA1* and *BRCA2* are the most common definable cause of inherited breast cancer. Cancer cells from patients with germline *BRCA1/2* mutations are deficient in the ability to repair double-strand DNA breaks through HRR (Roy et al 2012). This deficiency is presumed to underlie the observation that *BRCA1/2*-deficient cells are sensitive to interventions that promote double strand DNA breaks or cross-links, such as ionizing radiation and platinum based chemotherapeutic agents. It is also presumed to underlie the observation that *BRCA1/2*-deficient cells are sensitive to treatment with PARP inhibitors (Bryant et al 2005, Farmer et al 2005) which are presumed to force repair of single strand breaks (SSBs) towards the HRR pathway rather than the pathways that usually address SSBs. Phase I and proof-of-concept phase II studies have shown that PARP inhibitors have significant activity with limited toxicity when used as single agents in the treatment of *BRCA1/2m* breast and ovarian cancer (Audeh et al 2010, Fong et al 2009, Tutt et al 2010). In patients with breast cancer, who have progressed after anthracycline and taxane therapy, there are a number of potential cytotoxic treatments, with none offering a clear advantage over the others. The present study is an important step in defining the role of olaparib as a PARP inhibitor in metastatic HRR mutated (HRR*m*) TNBC patients. The study will assess the efficacy of olaparib monotherapy relative to combinations with inhibitors of DDR.

The scientific rationale and the available clinical data (see Section 1.2.1) support the investigation of olaparib as a therapeutic intervention for patients with metastatic germline or somatic *BRCAm* breast cancer. The purpose of this study is to compare the efficacy of 2 specific inhibitors of DDR in combination with olaparib with single agent olaparib in the *BRCAm* patient segment, but also beyond this in a broader group of patients with and without HRR mutations.

A proportion of sporadic TNBCs may have reduced *BRCA1* expression or *BRCA1* promoter methylation that results in a loss of *BRCA1* expression. It is estimated that as a result, up to 40-60% of sporadic TNBCs also have evidence of defective HR and therefore would benefit from PARP inhibitor treatment (Graeser et al 2010).

1.2 Rationale for study design, doses and control groups

1.2.1 Olaparib rationale

Olaparib is a potent PARP inhibitor approved both in the United States of America (USA) and the European Union (EU) for the treatment of patients with *BRCAm* ovarian cancers. Olaparib was granted Food and Drug Administration (FDA) approval in 2014 for the monotherapy treatment of patients with deleterious or suspected deleterious germline *BRCA* mutation (g*BRCAm*) (as detected by FDA approved test) advanced ovarian cancer who have been treated with 3 or more lines of chemotherapy. In the EU, olaparib is approved as maintenance treatment for women with platinum-sensitive relapsed ovarian cancer (including fallopian tube or primary peritoneal) with *gBRCAm* who responded to platinum-based chemotherapy. Olaparib proved efficacious for this indication based on a pre-defined subgroup analysis of a single efficacy study (D08119C00019 or Study 19) in 96 patients with *gBRCAm*, platinum-sensitive ovarian cancer who were in response to platinum-based chemotherapy. Patients were randomised 1:1 to receive either olaparib or placebo. Randomisation was stratified by the time of disease progression from the completion of the penultimate platinum therapy (6-12 months vs >12 months), objective response to the last platinum containing regimen prior to enrolment on study (complete response [CR] or partial response [PR]), and the ethnic descent of the patient. The primary efficacy analysis of Study 19 was Investigator-determined progression-free survival (PFS). In a pre-specified retrospective subgroup analysis of Study 19, there was improvement (HR 0.17) in PFS of the 96 patients with *gBRCAm* ovarian cancer randomised to olaparib treatment, with median PFS of 11.2 months in the olaparib arm and 4.1 months in the placebo arm. An exploratory analysis by AstraZeneca in Study 19 provided the early clinical evidence supporting the notion that patients without *BRCA* mutations but in other HRR genes (non *BRCA* gene mutations) have a preferential treatment benefit from olaparib maintenance therapy. In Study 19, mutation profiling by NGS of tumour tissue from 209 patients indicated that 54.5% of patients had deleterious or suspected deleterious *BRCA* mutations. Among the remaining, patients with no detected *BRCA* mutation (22% [21/95 patients]) had a deleterious mutation in non *BRCA* HRR genes including *ATM*, *BRIP1*, *CDK12*, *FANCA*, *FANCD2*, *FANCI*, *FANCL*, *RAD51B*, *RAD51C*, *RAD52*, *RAD54L*, and *XRCC3*. The rest of the 74 patients did not have any detectable deleterious mutations in any gene or had a variant of unknown significance. Patients with mutations in non *BRCA* HRR genes had a preferential treatment benefit from

olaparib maintenance therapy compared with patients with no evidence of *BRCA* or other HRR gene mutations. Separation of the KM curves for PFS in favour of olaparib was observed for the 21 patients with tumours that were non *BRCA* HRRm, but not in the 58 patients with tumours where no HRR mutation was detected (Hodgson et al 2015).

Olaparib monotherapy was investigated in a Phase 2 multicentre study in women with high-grade serous ovarian carcinoma (HGSOC) or TNBC receiving olaparib 400 mg bd capsules (Gelmon et al 2011). Patients were stratified according to *BRCA1* or *BRCA2* mutation or no known mutation. Ninety patients of the 91 enrolled received treatment (HGSOC n=64 and TNBC n=26). Of the HGSOC patients with *BRCA1* or *BRCA2* mutations, objective response was observed in 7/17 patients (41%; 95% CI 22%-64%). Response was observed in 11/46 patients (24%; 95% CI 14%-38%) without known mutations.

Olaparib monotherapy has been investigated in Phase 2 and Phase 3 studies in metastatic or advanced breast cancer. In the Phase 2 study, women with confirmed *BRCA1* and *BRCA2* mutation, with advanced breast cancer and a median of 3 prior chemotherapy regimens before entering the study were administered olaparib in two sequential dosing cohorts. Cohort 1 (n=27) were administered olaparib 400 mg capsules bd, and cohort 2 (n=27) were given an olaparib 100 mg capsule bd. In cohort 1 (400 mg bd), objective response was observed in 11 (41%) of 27 patients (95%; CI 25%-59%), and 6 (22%) of 27 patients (95%; CI 11%-41%) in cohort 2 (100 mg bd) (Tutt et al 2010). In the Phase 3 study, women with TNBC or ER/PR^{+} breast cancer (who were not eligible for further endocrine therapy) and confirmed *BRCA1* and *BRCA2* mutations were randomised to receive olaparib monotherapy (300 mg tablet bd) (n=205) or Physician's choice of chemotherapy (capecitabine, vinorelbine, or eribulin) (n=97). Median PFS of patients who were ER or PgR negative, as assessed by blinded central review, was 5.6 months for the olaparib arm compared with 2.7 months for the chemotherapy arm (HR=0.39, p<0.009). The ORR, as assessed by blinded central review, for all patients, was 59.9% for the olaparib arm (95%; CI 52.3%-67.4%), and 28.8% in the chemotherapy arm (95%, CI 18.3%-41.3%) (Krammer et al 2017).

In addition to the clinical benefit observed in patients with mutations in *BRCA1* and *BRCA2* genes, clinical benefit has also been described in ovarian cancer patients without *BRCAm* tumours but harbouring mutations in other HRR genes, such as *BRCA* associated proteins *BRIP1*, *PALB2* and those genes associated with DNA double strand break (DSB) repair such as Ataxia Telangiectasia mutated (*ATM)* (Bang et al 2013, Daugherty et al 2014).

The recommended tablet monotherapy dose is 300 mg bd, based on tolerability and tumour shrinkage data from study D0810C00024, in an advanced *gBRCA* mutated ovarian cancer population. This dosing regimen is expected to maintain plasma concentrations above the estimated mouse 90% inhibitory concentration and its upper 95% CI for tumour PARP inhibition across the full dosing interval, ie, 12 hours.

Further information on the pharmacokinetics (PK) and metabolism of olaparib is provided in the current version of the olaparib Investigator's Brochure (IB).

1.2.2 AZD1775+olaparib rationale (Treatment arm closed April 2019)

AZD1775 is an inhibitor of WEE1, a checkpoint protein tyrosine kinase. WEE1 phosphorylates and inhibits cyclin-dependent kinases 1 (CDK1) and 2 (CDK2), and is involved in regulation of the intra-S and G2/M cell cycle checkpoint arrest for pre-mitotic DNA repair (Parker and Piwnica Worms 1992). Normal cells ensure genomic integrity by repairing DNA that is damaged before cell cycle progression through these checkpoints. Phosphorylation is vital for regulation of the cell cycle and progress through the cell cycle depends on CDKs (De Witt Hamer et al 2011). CDK1 (also called cell division cycle 2, or CDC2) activity promotes the advancement from the G2 phase of the cell cycle into mitosis. In response to DNA damage, WEE1 inhibits CDK1 to prevent the cell from dividing until the damaged DNA is repaired (G2 checkpoint arrest). Inhibition of WEE1 is also expected to release a tumour cell from DNA damage-induced arrest of cell replication. Preclinical *in vitro* and *in vivo* experiments demonstrate that AZD1775 has synergistic cytotoxic effects when administered in combination with various DNA damaging agents that have divergent mechanisms of action, including the DNA damage induced by the treatment of an inhibitor of PARP such as olaparib.

AZD1775 is a potent inhibitor of WEE1 that has significant selectivity over other tested protein kinases. In *in vitro* studies, AZD1775 inhibits WEE1 activity and induces DNA damage as well as G2 checkpoint escape in cell-based assays. AZD1775 increases cytotoxicity when used in combination with DNA damaging agents, such as gemcitabine, cisplatin, carboplatin, and topotecan, in p53-deficient cell lines. In *in vivo* studies, AZD1775 was well tolerated and showed enhancement of anti-tumour efficacy by gemcitabine, carboplatin, cisplatin, 5-fluorouracil, and capecitabine in nude rat xenograft tumour models. Similarly, in nude mouse xenograft models, AZD1775 treatment resulted in significant tumour growth inhibition at tolerated doses, and also enhanced the anti-tumour growth effect of gemcitabine, carboplatin, and radiation therapy (see the most recent AZD1775 IB). In addition, *in vivo* data have demonstrated enhanced anti-tumour activity following treatment with the PARP inhibitor olaparib.

Given that PARP inhibition by olaparib traps PARP protein on DNA causing collisions with DNA replication forks (in actively replicating cells S-phase cells), “stalling” the progression of said replication fork and then its collapse (Pommier et al 2016), leads to DNA DSBs in S-phase (Fong et al 2009), it is predicted that *ATR* or WEE1 kinase inhibition combined with PARP inhibition may be synergistic and impair cancer cell survival. Preclinical data support this hypothesis, and the data from three different TNBC patient-derived explant models that have different levels of sensitivity to the AZD1775 and olaparib single agents all show enhanced tumour response (red lines) versus those of olaparib (blue lines) and AZD1775 monotherapy (gold lines).

CCI

The AZD1775 dose proposed in this study is based on the ongoing dose finding Phase Ib study (study code: D6010C00005) of AZD1775 and olaparib in patients with refractory solid tumours. The safety review of the AZD1775 175 mg bd 3 days on/4 days off, 2 weeks out of 3 in combination with olaparib 200 mg bd continuous was deemed tolerable. A total of 13 patients received this combination dose and schedule, with 1 dose limiting toxicity of Grade 4 thrombocytopenia and Grade 4 neutropenia observed out of 12 evaluable patients. This dose was declared as the maximum tolerated dose.

Early emerging safety data in the VIOLETTE study within the AZD1775 plus olaparib treatment arm using this dose and schedule, prompted a reduction in the starting dose for AZD1775 to 150mg bd 3 days on/4 days off, 2 weeks out of 3, in combination with olaparib 200 mg bd continuous. This dose was selected as it represented the previously defined next dose reduction level within the VIOLETTE protocol, and is aligned with the dose reduction guidelines for this dose cohort within the ongoing Phase Ib study mentioned above.

Preliminary PK data suggest that steady state trough concentration of AZD1775 at 175 mg and 150 mg bd exceeds the PK target of 240 nM. AZD1775 is a time dependent inhibitor of CYP3A4 and is expected to increase exposure of CYP3A4 substrates including Olaparib.

Based on preliminary PK and DDI data from 175 mg BID dose (n=23), in study D6010C00005, AZD1775 results in up to 33% increase in olaparib exposure in patients dosed with 200 mg bd olaparib. Refer to section 5.1.4 of investigator brochure for additional details. Because of this drug-drug interaction (DDI), the olaparib exposure at 200 mg bd is similar and within the variability seen with the 300 mg bd tablet dose when combined with 175 mg BID AZD1775 (Figure 1). At 150 mg BID dose (n=6, cohort 3.2 study D6010C00005), limited PK data is available suggesting minimal interaction with Olaparib (Table 1). It should be noted that PK estimates for AZD1775 have been observed to be higher in the Asian population as compared to the Western population (Section 5.1.6 of Investigator Brochure).

Table 1 Preliminary DDI summarized as ratio[(Day 3 PK (AZD1775 + Olaparib) over Day -1 PK (Olaparib alone)] of 200 mg BID Olaparib in patients with 175 and 150 mg BID AZD1775

AZD1775 Dose/Schedule	Olaparib Dose	N	AUC_{0-10} Ratio (range)	C_{max} Ratio (range)
175 mg BID, 3/4	200 mg BID	23	1.33 (0.738-2.57)	1.18 (0.85-2.11)
150 mg BID, 3/4	200 mg BID (days 1-14)	6	0.8915 (0.5-1.44)	0.908 (0.42-1.38)

The 200 mg BID dose of olaparib to be used in combination with AZD1775 is lower than the approved 300 mg BID. Based on the exposure response (PFS) analysis, although 300 mg BID tablet is statistically superior to the 200 mg BID tablet dose, the magnitude of the difference is of a small degree (data on file) . In addition, the olaparib steady state trough concentration (unbound) with and without AZD1775 is above the PAR IC95 throughout the dosing interval (Figure 1) and is expected to maintain the predicted efficacy as demonstrated by the pre-clinical data in Figure 1.

Following the ISRC meeting on 17 April 2019 a recommendation was made to close the AZD1775+olaparib treatment arm across all biomarker strata due to increased toxicity and no suggestion of benefit and that patients currently receiving treatment with AZD1775+olaparib treatment be offered the opportunity to continue treatment with olaparib monotherapy at the approved dose (300 mg bd). This recommendation was ratified by the AstraZeneca Unblinded Review Committee and implemented in protocol version 6.0.

Figure 1 Olaparib clinical steady state concentration compared with preclinical PDX PAR IC95

1.2.3 Ceralasertib+olaparib rationale

Olaparib and ceralasertib both inhibit key checkpoints within DDR pathways and individually may be able to reduce the rate of DNA repair in cells, causing cell death. Therefore, the mechanistic rationale to combine these compounds is that by inhibiting two repair pathways simultaneously, the rapidly replicating cancer cells have fewer ways to repair damaged DNA, leading to cell death.

Ceralasertib is a potent, selective inhibitor of the serine/threonine-specific protein kinase, *ATR*, with good selectivity against other phosphatidylinositol 3-kinase-related kinase family members. This compound is being developed as an oral anti-tumour agent in patients with disease that may be dependent upon *ATR* function for DNA repair; an example being tumours that are deficient of the serine/threonine-specific protein kinase, *ATM*.

During DNA replication, *ATR* is recruited to regions of single stranded DNA coated with replication protein A caused by stalled replication forks (which can progress to lethal DSBs if left unrepaired) and following the resection of DNA DSB damage. Recruitment and activation of *ATR* leads to cell cycle arrest in the S phase while the DNA is repaired and the stalled replication fork resolved, or nuclear fragmentation and entry into programmed cell death/apoptosis (Chan et al 2002, Cimprich and Cortez 2008). Loss of *ATR* function leads to the inability to resolve stalled replication forks, the accumulation of DNA damage and rapid cell death exemplified by nuclear fragmentation. *ATR* deletion is lethal in embryonic mice, however severe *ATR* hypomorphism is tolerated in humans leading to Seckel Syndrome. Normal cells from patients with Seckel Syndrome have reduced *ATR* function and show

extensive DNA breaks when subjected to replication stress (ASCO-CAP, Ajani et al 2007, Alderton et al 2004).

ATR is responsible for sensing stalled replication forks and activating (via phosphorylation) effector proteins to slow DNA replication, elicit S-phase cell cycle arrest (via CHK1), maintain fork integrity and restart replication once resolved. Inhibition of ATR kinase activity leads to the inability to resolve stalled replication forks resulting in accumulation of DSBs as more forks lose integrity and collapse. If damage is sufficiently high and persistent, this leads to cell death. Normally, the related DNA DSB activated kinase ATM can work in conjunction with ATR as forks collapse to DSBs to efficiently repair the damage and maintain genomic integrity. This interplay between ATM and ATR creates a "synthetic lethality" like dependency where loss of ATM pathway function leads to a greater reliance on ATR for a cell to maintain cell viability. In support of this, pre-clinical in vitro and in vivo studies with ATR inhibitors has shown preferential activity in cancer models which have lost of ATM function and related DDR pathways (Kwok et al 2016, Min et al 2016, George et al 2017). In addition, cancers with high levels of on-going replication stress and ATR activation either endogenously (eg, Myc oncogene driven tumours) or exogenously (eg, through radiation, chemotherapy or PARP inhibitor induced DNA damage at DNA replication forks) would also be more susceptible to ATR inhibition (Foote et al 2015, Vendetti et al 2015, Dillon et al 2017).

Olaparib acts via two mechanisms to elicit synthetic lethality effect: (i) inhibition of SSB repair and increasing the number of single stranded DNA nicks and (ii) "trapping" of PARP-DNA complexes both of which create DNA replication fork damage (replication stress) and DNA DSB formation (Murai et al 2012, Pommier et al 2016), which are activation signals for *ATR* and *ATM*-dependent repair. Cells which have functional defects in *BRCA*, *ATM* or *ATR* (or pathway related genes) are predicted to be highly sensitive to olaparib as a monotherapy. Indeed, pre-clinical studies in which *ATM* or *ATR* gene expression are specifically down-regulated have shown significantly increased sensitivity to PARP inhibitors when compared to their matched control cells (McCabe et al 2006, Lord and Ashworth 2015, Lord et al 2008, Turner et al 2008, Bajrami et al 2014). Consistent with these findings, preclinical studies combining ceralasertib with olaparib have shown synergistic combination responses (versus single agent activity) in both *BRCA* mutant and non *BRCA* TNBC patient-derived explant models (see figure below).

The addition of an *ATR* inhibitor such as ceralasertib to olaparib would be expected to be particularly efficacious in *BRCAm* breast cancer, but the combination might well lead to anti-tumour activity in tumours which do not harbour *BRCA* mutations and has demonstrated anti-tumour activity in non *BRCA* mutated preclinical models, and so investigation of the combination in patients with *BRCAm* or without *BRCAm* breast cancer is well justified. The results from this study may form the basis for decisions for future studies.

Similar data is available for the ceralasertib and olaparib combination (blue lines) also showing enhanced tumour response versus ceralasertib (red lines) or olaparib (green lines) alone in the same three TNBC patient derived models. This includes enhanced response to the combination versus single agents in the non *BRCAm* HBCx-9 tumour model (far left panels).

CCI

The ceralasertib dose proposed in this study is based on Module 2 of the ongoing Phase I Study (Study code D5330C00004) of ceralasertib and olaparib in patients with advanced malignancies. The recommended Phase 2 dose has been established as ceralasertib 160 mg od administered days 1-7 in combination with olaparib 300 mg bd administered continuously in a 28-day cycle. The dosing schedule of 7 days on, 21 days off within each treatment cycle was supported by the PK-pharmacodynamics (PDx) model of thrombocytopenia, predicting a period of 21 days free of drug to achieve a full platelet recovery. The recommended dose 160 mg od was predicted to maintain ceralasertib mean steady state concentrations above the estimated IC90 threshold (based on ATR enzyme inhibition assay in LoVo cells) and the GI90 threshold (based on the cellular growth inhibition activity in LoVo cells) across the full dosing interval i.e. 24h. Please refer to ceralasertib IB for further information around the *in vitro* threshold values. In addition, this daily dose level was associated with a decrease in peripheral monocytes in most of the patients and the preliminary blood cell count data from D5330C00004 and D5330C00002 studies suggested this decrease to be ceralasertib specific and dose dependent (monocyte decrease was not observed with either single agent olaparib or durvalumab). Monocytes have been characterized as being deficient in DNA base excision repair and PARP1 expression (Bauer et al 2011), suggesting an on-target synthetic lethal effect of ceralasertib mediated ATR inhibition in this cell type. Utilizing the monocyte decrease as a quantitative measure of ceralasertib pharmacological activity, the recommended Phase 2 dose of 160 mg od D1-7 was driven by maintaining maximally active exposure consistent with manageable safety.

Details on the latest non clinical and clinical safety and efficacy data for ceralasertib are presented in the latest version of the ceralasertib Investigator's Brochure.

1.3 Benefit/risk and ethical assessment

1.3.1 Potential benefits and risks for olaparib

Olaparib is approved as follows:

EU indication: Lynparza is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed *BRCA*-mutated (germline and/or somatic) high grade

serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (CR or PR) to platinum-based chemotherapy.

US indication: Lynparza is indicated as monotherapy for patients with deleterious or suspected deleterious germline *BRCA*-mutated (as detected by an FDA-approved test) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy and for patients with deleterious or suspected deleterious *gBRCAm*, human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer who have previously been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting. Patients with hormone receptor-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine treatment. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza.

Ovarian cancer and other advanced cancers are serious and life-threatening diseases and new medicines are needed. There is a large unmet need to minimise the toxicity burden for patients, prolong progression-free survival (PFS) and delay the need for next-line chemotherapy and the associated toxicities.

A robust biological rationale underpins the investigation of the PARP inhibitor olaparib in cancer patients with homologous recombination deficiencies (HRDs) including tumours with a *BRCA* mutation. Approximately 15% of ovarian cancer patients and 5% of breast, pancreatic and prostate cancer patients have inherited mutations of *BRCA1* or *BRCA2*. In addition to genetic loss of *BRCA* function, it has been suggested that a further ~20% of tumours display so-called "BRCAness" (Turner et al 2004; Chan et al 2002). Furthermore, reduced function of other key proteins in the homologous recombination pathway similarly results in increased sensitivity to PARP inhibition and enhancement of chemotherapy and radiotherapy treatments. For these reasons, PARP inhibition represents a novel approach to anti-tumour therapy and may address an unmet need in patients with *BRCA* associated cancer. In addition, the use of PARP inhibitors in combination has confirmed that an enhancement of the anti-tumour activity of radiation and DNA damaging cytotoxic agents occurs (Virag and Szabo 2002, Nguewa et al 2005). Identification of safe and effective doses of olaparib in combination regimens offers potential in many tumour types.

Data from the clinical development programme demonstrate that olaparib appears to be active and generally well tolerated in patients with advanced solid tumours including those with *BRCA* mutated cancers. Olaparib maintenance therapy (capsule formulation) has demonstrated, in a well-controlled randomised Phase II study (Study D0810C00019), a clinically meaningful prolongation of PFS in the subgroup of 136 patients with *BRCA* mutated ovarian cancer providing a 6.9 month prolongation of median PFS over placebo (PFS HR 0.18), together with a meaningful delay to the time the next cancer treatment is required (HR 0.33; median prolongation of 9.4 months longer than placebo; 15.6 months olaparib vs 6.2 months placebo).

Data from Study D0816C00002 (the SOLO2 study) have confirmed the results of Study 19 using the olaparib tablet formulation (300 mg bd) as maintenance monotherapy in platinum-sensitive relapsed ovarian cancer in patients carrying a deleterious or suspected

deleterious *gBRCA* mutation. Investigator assessed PFS (the primary endpoint) following olaparib maintenance therapy was significantly longer compared with the placebo group (HR 0.30; 95% CI 0.22-0.41; p<0.0001). Median PFS on the placebo arm was 5.5 months versus 19.1 months on the olaparib arm. The Investigator assessed PFS findings were confirmed by BICR of the data. Overall survival data are immature. The tolerability profile of olaparib is well characterised and suitable for long term dosing as a monotherapy. Adverse drug reactions (ADRs) considered to be associated with administration of olaparib monotherapy include: haematological effects (anaemia, neutropenia, lymphopenia, leukopenia, thrombocytopenia, mean cell volume [MCV] elevation); increase in blood creatinine; nausea and vomiting; decreased appetite; diarrhoea; dyspepsia; stomatitis; upper abdominal pain; dysgeusia; fatigue (including asthenia); headache; dizziness; rash; hypersensitivity, dermatitis and dyspnoea. Most of these events were generally mild or moderate in intensity.

Data from Phase I dose escalation studies of olaparib in combination with various chemotherapy agents indicate an increase in bone marrow toxicity greater than expected if the agents would be administered alone. When this type of toxicity has occurred it has been managed by routine clinical practice including dose delays, dose reductions, intermittent dosing and/or the use of supportive care measures, including granulocyte colony-stimulating factor (G-CSF).

In a relatively small number of patients across the development programme, pneumonitis, myelodysplastic syndrome (MDS)/acute myeloid leukaemia (AML) and new primary malignancies have been observed. Evaluation of all available data has not provided sufficient evidence to support a causal relationship between olaparib and these events. These are categorised as important potential risks for olaparib and are being kept under close surveillance. Many patients have already received DNA-damaging chemotherapy and the benefits that patients with HRD tumours may receive from olaparib are considered to outweigh the potential risks.

The commonly reported low severity grade AEs are routinely managed by oncologists treating cancer patients. The low grade, intermittent nausea and vomiting can be treated empirically and antiemetic prophylaxis is not required. Haematological changes including anaemia should be routinely monitored for using standard assessments of haematological laboratory parameters. Where clinically necessary, ADRs can be managed by interrupting or reducing the olaparib dose, treating symptomatically with standard procedures (eg, antiemetics for nausea and vomiting, blood transfusions for anaemia) or in rare cases by permanently discontinuing olaparib treatment.

The molecular targeting of olaparib to specific subsets of tumours may provide an opportunity for more effective and potentially less toxic cancer treatment for some patients compared with currently available regimens. AstraZeneca believes that olaparib continues to demonstrate an overall positive benefit-risk balance to support its further clinical evaluation in patients with advanced cancers, and as a neo-adjuvant and post-chemotherapy adjuvant treatment option for patients with BRCA mutated cancers. Overall, based on the available data on efficacy and

safety, AstraZeneca believes that olaparib continues to demonstrate positive benefit-risk balance in the studied cancer population.

Further details about Olaparib safety and tolerability are provided in the olaparib IB.

1.3.2 Potential benefits and risks for AZD1775 (treatment arm closed April 2019)

AZD1775 is currently being investigated for the treatment of patients with advanced solid tumours with genetic deficiencies in DNA repair mechanisms. In the advanced cancer setting, prolonged survival rates are very low and there is a considerable unmet clinical need for novel therapeutic agents. The primary objectives of studies with AZD1775 to date have been to determine the safety and tolerability of AZD1775 in combination with other cancer treatments, or as a monotherapy, and although there can be no final benefit-risk assessment made at this point in time, preclinical data, and emerging clinical data with AZD1775, support the hypothesis that WEE1 kinase inhibition may be a valid target for treatment of tumours. The preclinical safety profile, and emerging clinical data for AZD1775, did not identify any risks that would have precluded investigation in this setting, and monitoring has been, and still is, in place for those risks deemed to be most likely or serious, and for those that require further investigation.

Data from the non-clinical studies and the emerging data from the clinical development programme show that AZD1775 has a manageable safety profile in an advanced cancer population. Adverse drug reactions to AZD1775 monotherapy include: anaemia, neutropenia and febrile neutropenia, thrombocytopenia, QTc prolongation, gastrointestinal events such as dyspepsia, diarrhoea, nausea and vomiting (with or without dehydration or serum electrolyte decreases), as well as decreased appetite. Potential risks with AZD1775 monotherapy include asthenia/fatigue, febrile neutropenia, gastrointestinal haemorrhage, lymphopenia/lymphocytes count decreased, leukopenia/WBC count decreased, myalgia, stomatitis, sepsis and transaminases elevation. Refer to the AZD1775 IB for information on the assessment of potential and known risk.

AZD1775 and olaparib have some overlapping clinical toxicities in their AE profiles, namely gastrointestinal toxicities (eg, diarrhoea, nausea and vomiting) and haematological toxicities (eg anaemia, neutropenia, and thrombocytopenia). The emerging safety profile seen in a current dose escalation study D6010C00005 (REFMAL 384) where various combination dosing regimens are being explored with AZD1775 (125-175 mg bd and 250 mg every day [qd]) in combination with olaparib (100-300 mg bd 14 or 21 days) the occurrences of diarrhoea, nausea, and vomiting is of similar incidence and severity to AZD1775 monotherapy. However, haematological toxicities such as anaemia, neutropenia and thrombocytopenia were seen at greater incidence and severity when AZD1775 was combined with olaparib compared to olaparib monotherapy. Early emerging safety data in the VIOLETTE study within the AZD1775 plus olaparib treatment arm using the AZD1775 175mg bd 3 days on/4 days off, 2 weeks out of 3, in combination with olaparib 200 mg bd continuous prompted a reduction in the starting dose of AZD1775 to 150mg bd. This dose was selected as it represented the previously defined next dose reduction level within the Violette protocol, and is aligned with the dose reduction guidelines for theAZD1775 175mg bd 3 days

on/4 days off, 2 weeks out of 3, in combination with olaparib 200 mg bd continuous dosing schedule used in an ongoing phase Ib dose finding trial for the combination of AZD1775 and olaparib (REFMAL384).

In addition to the aforementioned overlapping toxicities, fatigue was seen in a marginally higher percentage of patients when AZD1775 was combined with olaparib in comparison to olaparib monotherapy, and the severity of the fatigue seen was also marginally higher when these two compounds were combined.

Investigations of AZD1775 when combined with chemotherapy show the drugs have been tolerated and have shown efficacy (see AZD1775 IB). The preclinical and clinical data of AZD1775 and olaparib support the exploration of the effectiveness of this combination in patients with TNBC. An analysis of overall risks and benefits supports the administration of oral AZD1775 and olaparib according to this clinical protocol.

Information on clinical efficacy and safety data from AZD1775 monotherapy and combination therapy studies can be found in Sections 5.2 and 5.4 of the current AZD1775 IB. The identified risks (expected events) for AZD1775 are described in section 5.4 (Emerging Safety Profile) of the IB. Section 6.4 (Risk Management) of the IB provides specific advice to the investigator regarding standard safety practices to be followed when handling and administering AZD1775.

Following the ISRC meeting on 17 April 2019 a recommendation was made to close the AZD1775+olaparib treatment arm across all biomarker strata and that patients currently receiving treatment with AZD1775+olaparib treatment be offered the opportunity to continue treatment of olaparib monotherapy at the approved dose (300 mg bd). This recommendation was ratified by the AstraZeneca Unblinded Review Committee and implemented in protocol version 6.0.

1.3.3 Potential benefits and risks for ceralasertib

Ceralasertib is currently being investigated in combination with olaparib in patients with advanced malignancies in Module 2 of Study D5330C00004. The primary objective of studies with ceralasertib to date has been to determine the safety and tolerability of ceralasertib in combination with other cancer treatments, including cytotoxic chemotherapy, olaparib, durvalumab, radiation and as monotherapy. The RP2D in combination with olaparib has been established and preliminary signs of efficacy have been observed in patients with *BRCA* mutated TNBC.

The rationale for the current study is supported by preclinical data in breast cancer models showing that, where tumour cells are dependent upon *ATR* for DNA repair through defects in HRR, ceralasertib increases tumour sensitivity to olaparib therapy. The addition of a second DDR modifier to olaparib, such as ceralasertib, is justifiable as there is the potential to increase the anti-tumour effect associated with olaparib as a mechanism to increase responses in patients with *BRCAm* where the activity of olaparib is established, and in patients with other (non-*BRCA1* and *BRCA2*) HRR-related genes which may lead to HRR defects in tumour

cells. These defects are associated with a reduced innate ability to repair DNA. Patients with sporadic tumours that share molecular features of *BRCA*-mutant tumours, that is, those with '*BRCA*ness' may also respond to this therapeutic approach and share the same therapeutic vulnerabilities as those seen with *BRCAm* and /or HRR-related genetic alterations (Lord and Ashworth 2015).

Data from the non-clinical studies and the emerging data from the clinical development programme show that ceralasertib has a manageable safety profile in an advanced cancer population, and a number of potential risks which have not been causally related to ceralasertib and are being monitored in ongoing clinical trials. The emerging safety profile from patients receiving treatment with ceralasertib and olaparib has demonstrated very common AEs (≥1/10 according to CIOMS III frequency classification) considered possibly related to ceralasertib and/or olaparib by the Investigator of anaemia and fatigue. Common adverse events (≥1/100 to <1/10) considered possibly related include nausea, neutropenia, thromobocytopenia, vomiting, anorexia, dizziness, diarrhoea, thrombocytopenia, leucopenia, increase in blood creatinine and asthenia. Potential risks with ceralasertib include reproductive and genotoxicity, hepatic toxicity, cardiovascular risk and possible DDIs. As of the data cut-off of 13-Jun-2019, ceralasertib has been administered to 425 patients either as monotherapy or in combination with other agents. In this ongoing study, the study arm allocation of an additional 133 patients was unavailable at the time of the data cut-off date.

Effects on bone marrow are anticipated in the clinic and may occur in the second or third week of dosing but may also arise after the first cycle resulting in dosing delays. These events are deemed schedule limiting, rather than dose limiting toxicities as the main issue is a delayed recovery of the platelets. Myelosuppression has been successfully managed with dose interruptions, dose reductions (dose and schedule) and supportive measures such as blood transfusions. Haematology and biochemistry blood counts will be monitored each cycle in the clinic.

The current study has been designed to allow the assessment of ceralasertib in combination with olaparib in three molecular strata in patients with TNBC. Clinical experience of this combination has demonstrated tolerability and preliminary efficacy, and the exploration of this combination in patients with advanced TNBC is considered to have a positive benefit-risk profile.

Refer to the ceralasertib Investigator's brochure for further information.

1.3.4 Benefit-risk Summary and Overall Conclusions

Inhibiting DDR is an established approach to cancer treatment. The use of targeted agents that inhibit PARP, WEE1 and *ATR*, which are involved in DDR provides a potential new treatment option for patients with advanced TNBC. The emerging data form the clinical development programmes have identified the above risks which will be assessed, monitored and addressed accordingly during the current study. Risk minimisation strategies and detailed toxicity management guidelines are incorporated into the clinical protocol and toxicity is

considered clinically manageable with the measures in place. The study sponsor will continue to monitor the clinical and nonclinical data for emerging safety information.

1.4 Study Design

This is a prospective, open label, randomised, multi-centre Phase 2 study that will assess the efficacy and safety of olaparib monotherapy versus olaparib in combination with an inhibitor of ATR (ceralasertib) and olaparib monotherapy versus olaparib in combination with an inhibitor of WEE1 (AZD1775) in second or third line setting in patients with TNBC prospectively stratified by presence/absence of qualifying tumour mutation in genes involved in the HRR pathway. The study patient population will be stratified as described below:

- stratum A: patients with mutations in *BRCA1* or *BRCA2* (*BRCAm*)
- stratum B: patients with mutations in any of the following CCI genes involved in the HRR pathway (CCI and no mutation in *BRCA1* and no mutation in *BRCA2*
- stratum C: patients that have no detected tumour mutations in any of the CCI HRR genes mentioned above.

Following the ISRC meeting on 17 April 2019 a recommendation was made to close the AZD1775+olaparib treatment arm across all biomarker strata and that patients currently receiving treatment with AZD1775+olaparib treatment be offered the opportunity to continue olaparib monotherapy at the approved dose (300 mg bd). This recommendation was ratified by the AstraZeneca Unblinded Review Committee and implemented in protocol version 6.0. All patients randomized to this arm discontinued AZD1775 and continued on olaparib monotherapy increasing to the approved dose at the start of their next treatment ensuring a minimum 10 day wash out period from AZD1775 to olaparib 300 mg bd dosing to avoid DDI.

Within each stratum A, B and C, there will be further stratification by whether the patient received prior platinum-based therapy (yes/no).

The 3 treatment arms are:

Treatment Arm 1 – 300 mg bd olaparib continuous (28-day cycle)

Treatment Arm 2 – 160 mg od ceralasertib Days 1-7 + 300 mg bd olaparib continuous (28-day cycle)

Treatment Arm 3 – 150 mg bd AZD1775 Days 1-3 and 8-10 + 200 mg bd olaparib continuous (21-day cycle). This treatment arm was closed following the ISRC meeting on the 17 April 2019.

Due to the different schedules of administration of each of the treatment options as well as their different toxicity profiles, the study cannot be blinded. Given the open label design of

the study, efforts will be made to ensure robustness of the primary endpoint assessment and to avoid any unnecessary unblinding of the operational study team.

Two-stage consent process

Potentially suitable TNBC patients will be invited to consent to a Screening Part 1 process and patients must consent to provide a suitable FFPE tumour block, or tissue sections, that meets the tissue specifications outlined in the Laboratory Manual, for central HRR mutation testing on the Lynparza HRR assay.

The first stage consent can be obtained outside the 28-day screening window and is a consent for access to either a tumour tissue block or section of the archival diagnostic sample for mutation analysis.

Stage 1 consent (screening)

Patients must provide consent to the provision of a tumour sample suitable for the prospective central Lynparza HRR assay testing. Samples that meet the tissue specifications outlined as specified in the Laboratory Manual will be shipped at screening Part 1 to FMI (Cambridge, MA, USA) to determine HRR status.

If a patient has a previously confirmed qualifying (deleterious or suspected deleterious) mutation in any of the [redacted] HRR genes, the patient may meet biomarker testing requirements provided all of the following conditions are met:

1. Patients must consent to access to the genetic report generated using a test verified and validated in line with local regulations, within a GCP laboratory (including the FoundationOne® assay). The presence of a deleterious or suspected deleterious mutation in any of the specified [redacted] HRR genes. Results of the mutation status will be shared with AstraZeneca prior to patient randomisation.

2. Patients must consent to the provision of sufficient FFPE prepared tumour sample (block or sections). The tumour sample will be collected for retrospective central assessment of HRR status using the Lynparza HRR assay. The patient is not required to wait for the results of the Lynparza HRR assay to proceed with Screening Part 2 and randomisation, assuming all other eligibility criteria are met. The tumour sample for central confirmation should be shipped to FMI upon randomisation.

All patients must sign the stage 1 consent (screening part 1) before signing the stage 2 consent (screening part 2).

Stage 2 consent (main study)

Patients with TNBC and with known qualifying *BRCAm*, non *BRCAm* HRR*m* and non HRR*m* status will be offered the option of consenting to the main part of the study within the 28-day screening period.

Approximately 450 patients will be randomised (using randomisation ratio 1:1:1) to olaparib monotherapy, olaparib+ceralasertib or olaparib+AZD1775. Following the closure of the olaparib+AZD1775 arm in April 2019 the total number of patients randomised will be lower (approximately 350 patients).

The randomisation scheme will be stratified based on:

- stratum A: patients with mutations in *BRCA1* or *BRCA2* (*BRCAm*)
- stratum B: patients with mutations in any of the following CCI genes involved in the HRR pathway (CCI) and no mutation in *BRCA1* and no mutation in *BRCA2*
- stratum C: patients that have no detected tumour mutations in any of the CCI HRR genes mentioned above.
- tumour biomarker strata A, B, C defined above
- patient's prior platinum-based therapy (no / yes).

The 3 strata will be capped to achieve approximately 150 patients within each stratum (approximately 50 patients per treatment arm). Following the closure of the olaparib+AZD1775 arm, fewer than 50 patient per stratum had been randomised to this arm.

Please refer to the study flow chart (Figure 2).

Figure 2 Study flow chart

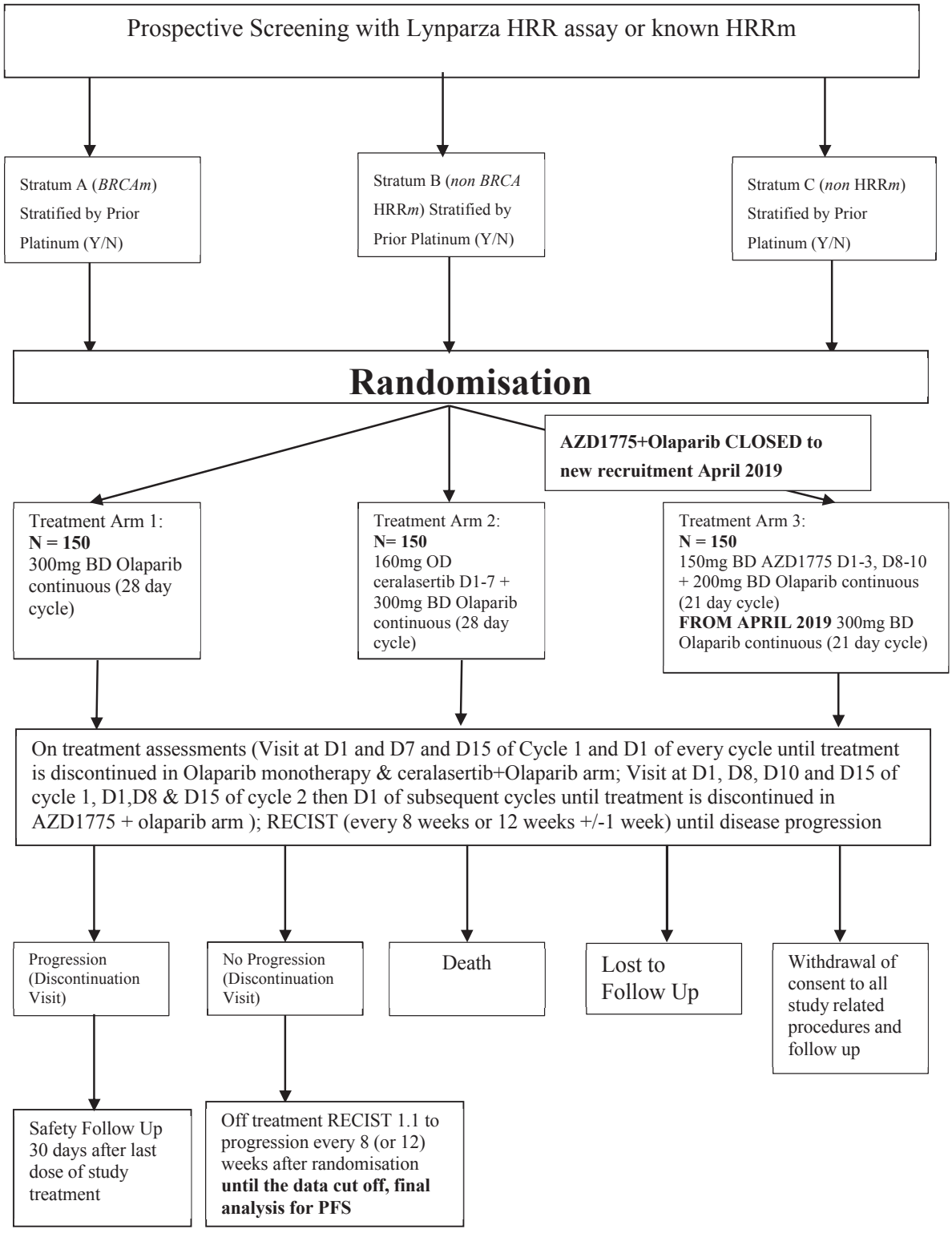
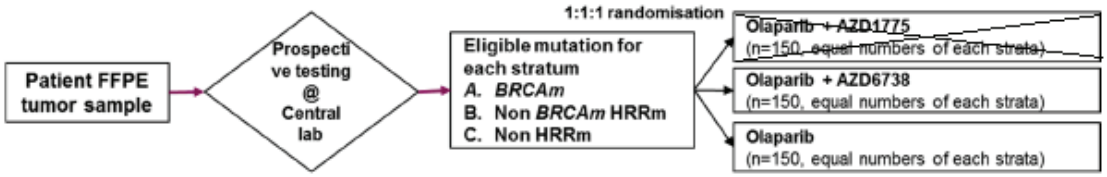


Figure 3 Diagnostic journey



- Note: Stratum A: *BRCAm*, stratum B: non *BRCAm* HRR*m* stratum C: non HRR*m*. The AZD1775+olaparib treatment arm was closed following the ISRC meeting on the 17 April 2019.

1.5 Study governance and oversight

1.5.1 Unblinded Review Committee

An AstraZeneca Data Monitoring Committee (AZ URC) will be convened and will conduct a review of the planned interim efficacy analyses. Safety will also be reviewed at this time.

Full details of the AZ URC procedures and processes can be found in the AZ URC Charter.

1.5.2 Independent Safety Review Committee

An independent Safety Review Committee (ISRC) will monitor safety and tolerability in the study at regular intervals.

Full details of the ISRC procedures, processes and potential recommendations can be found in the ISRC Charter.

2. STUDY OBJECTIVES

Study objectives are defined for the following patient populations:

- "*BRCAm*" = patients from stratum A
- "HRR*m*" = patients from stratum A and patients from stratum B
- "Non *BRCAm* HRR*m*" = patients from stratum B
- "All" = patients from any stratum
- "Non HRR*m*" = patients from stratum C

2.1 Primary objective

Patient Population	Primary Objective	Outcome Measure
• *BRCAm* • Non *BRCAm* HRR*m* • Non HRR*m*	To assess the efficacy of the combination of ceralasertib+olaparib and the combination of AZD1775+olaparib compared with olaparib monotherapy by assessment of PFS	PFS using BICR according to RECIST 1.1 Sensitivity analysis of PFS using Investigator assessments according to RECIST 1.1

2.2 Secondary objectives

Patient Population	Secondary Objectives	Outcome Measures
• HRR*m* • All	To assess the efficacy of the combination of ceralasertib+olaparib and the combination of AZD1775+olaparib compared with olaparib monotherapy by assessment of PFS	PFS using BICR according to RECIST 1.1 Sensitivity analysis of PFS using Investigator assessments according to RECIST 1.1
• *BRCAm* • HRR*m* • Non *BRCAm* HRR*m* • All • Non HRR*m*	To assess the efficacy of the combination of ceralasertib+olaparib and the combination of AZD1775+olaparib compared with olaparib monotherapy in terms of • ORR	Objective response using BICR according to RECIST 1.1 Sensitivity analysis of objective response using Investigator assessments according to RECIST 1.1
• *BRCAm* • Non *BRCAm* HRR*m* • Non HRR*m*	To assess the efficacy of the combination of ceralasertib+olaparib and the combination of AZD1775+olaparib compared with olaparib monotherapy in terms of • DoR • tumour change	DoR and tumour change using BICR according to RECIST 1.1 Sensitivity analysis of DoR, and tumour change using Investigator assessments according to RECIST 1.1

Patient Population	Secondary Objectives	Outcome Measures
• *BRCAm* • HRR*m* • Non *BRCAm* HRR*m* • All • Non HRR*m*	To assess the efficacy of the combination of ceralasertib+olaparib and the combination of AZD1775+olaparib compared with olaparib monotherapy in terms of OS	Time to death for any cause
• *BRCAm* • HRR*m* • Non *BRCAm* HRR*m* • All • Non HRR*m*	To compare the efficacy of the combination of ceralasertib+olaparib with the combination of AZD1775+olaparib in terms of • PFS • ORR	PFS and objective response using BICR according to RECIST 1.1 Sensitivity analysis of PFS and objective response using Investigator assessments according to RECIST 1.1
• *BRCAm* • Non *BRCAm* HRR*m* • Non HRR*m*	To compare the efficacy of the combination of ceralasertib+olaparib with the combination of AZD1775+olaparib in terms of • DoR • tumour change	DoR and tumour change using BICR according to RECIST 1.1 Sensitivity analysis of DoR and tumour change using Investigator assessments according to RECIST 1.1
• *BRCAm* • HRR*m* • Non *BRCAm* HRR*m* • All • Non HRR*m*	To compare the efficacy of the combination of ceralasertib+olaparib with the combination of AZD1775+olaparib in terms of OS	Time to death for any cause
• All	To explore the frequency of and describe the nature of tumour HRR (including *BRCA*) mutation(s) in tumour samples and to compare this with germline HRR (including *BRCA*) mutation status	Mutation status of CCI genes
• All	To assess exposure to olaparib ceralasertib and AZD1775 in all patients	$C_{min\ ss}$

2.3 Safety objectives

Patient Population	Safety Objective	Outcome Measure
• All	To assess the safety and tolerability of the combination of ceralasertib+olaparib and the combination of AZD1775+olaparib compared with olaparib monotherapy	• AEs (severity graded by CTCAE v4.03) • laboratory tests (clinical chemistry, haematology and urinalysis) • vital signs (pulse and BP) • ECG data • ECOG PS (see Appendix F)

2.4 Exploratory objectives

Not all data generated as part of exploratory analyses will be included in the Clinical Study Report (CSR) and these analyses will be reported separately.

Patient Population	Exploratory Objectives	Outcome Measure
• All	CCI	CCI
• *BRCAm* • HRR*m* • Non *BRCAm* HRR*m* • All • Non HRR*m*	CCI	CCI
• All	CCI	CCI

Patient Population	Exploratory Objectives	Outcome Measure
• All	CCI [redacted]	CCI [redacted]

3. PATIENT SELECTION, ENROLMENT, RANDOMISATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study prior to randomisation. **Under no circumstances can there be exceptions to this rule.**

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

Patients who already know they have a mutation in any of the defined CCI [redacted] HRR genes that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function) must fulfil all of the criteria below.

At Screening Part 1, prior to HRR mutation testing being carried out, the criteria marked with an asterisk (*) must be fulfilled by the patients who do not have a known HRRm status and are being considered for this study. Prior to performing the HRR testing, an Investigator judgement of a patient's potential eligibility for the study should be made according to details within Table 3 and by reviewing the inclusion/exclusion criteria.

Any patient who fulfils the eligibility criteria for the HRR test is required to have their eligibility assessed again prior to randomisation.

3.1 Inclusion criteria

For inclusion in the study patients should fulfil the following criteria:

1. * Provision of informed consent prior to any study specific procedures

2. * Patients must be male or female ≥18 years of age

3. Progressive cancer at the time of study entry

4. * Histologically or cytologically confirmed TNBC at initial diagnosis with evidence of metastatic or incurable advanced locoregional disease (defined as ER and PgR negative [IHC nuclear staining <1% positive] and HER2 negative [IHC 0, 1+ or IHC 2+ with corresponding ISH non-amplified of ratio less than 2.0 or ISH non-amplified ratio less than 2.0] as per ASCO-CAP HER2 guideline recommendations 2013 (ASCO-CAP). Note: An Allred score of 0-2 is acceptable however for a score of 2 the Proportion score must be checked to make sure it is 1 (≤1% cells are ER positive).

5. * Patients must have received at least 1 and no more than 2 prior lines of treatment for metastatic or incurable advanced locoregional disease with an anthracycline (eg, doxorubicin, epirubicin) and/or a taxane (eg, paclitaxel, docetaxel) unless contraindicated, in either the neo-adjuvant, adjuvant or metastatic setting.

   * Patients who have received platinum (cisplatin or carboplatin, either as monotherapy or in combination) for advanced breast cancer are eligible to enter the study provided there has been no evidence of disease progression during the platinum chemotherapy.

   * Patients who have received prior platinum based chemotherapy are eligible if platinum was given either as potentially curative treatment for a prior non breast cancer (eg, ovarian cancer) with no evidence of disease for ≥5 years prior to study entry or as adjuvant/neoadjuvant treatment for breast cancer provided at least 12 months have elapsed between the last dose of platinum-based treatment and randomisation

6. Confirmed presence of qualifying HRR mutation or absence of any HRR mutation in tumour tissue by the Lynparza HRR assay.

   – FFPE tumour tissue blocks are required for each patient, but if not available, tissue sections are accepted. At least twenty (20) (thirty [30] preferable) unstained sections without cover slips must be submitted to ensure sufficient material for the prospective Lynparza HRR testing to determine study eligibility and research that will aid understanding of the patient population relative to treatment with DDR and other cancer agents.

   – If a patient has a previously known qualifying *BRCA1/2* mutation or other HRR mutation, then the patient can be invited to consent to the full study. The patient will need to consent to provide an archival tumour block or tissue sections for central assessment of the HRR mutation status.

7. At least one measurable lesion that can be accurately assessed at baseline by computed tomography (CT) (magnetic resonance imaging [MRI] where CT is contraindicated) and is suitable for repeated assessment as per RECIST 1.1.

8. Patients must have normal organ and bone marrow function measured within 28 days prior to randomisation as defined below:

   (a) Haemoglobin (Hb) ≥10.0 g/dL with no blood transfusions (packed red blood cells) in the past 28 days

   (b) Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L

   (c) Platelet count ≥100 x 10^9/L with no platelet transfusions in the past 28 days

   (d) Total bilirubin ≤1.5 x institutional upper limit of normal (ULN) unless the patient has documented Gilbert's Syndrome

   (e) Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ≤2.5 x institutional ULN unless liver metastases are present in which case they must be ≤5 x ULN

   (f) Patients must have creatinine clearance (CrCl) of ≥51 mL/min estimated or measured using standard methodology at the investigating centre (i.e. Cockcroft-Gault, MDRD, CK-EPI, EDTA or 24 hr urine):

   $$\text{Estimated CrCl} = \frac{(140 - \text{age [years]}) \times \text{weight (kg)}}{\text{serum creatinine (mg/dL)} \times 72} \quad (\times F)^a$$

   [a] where F=0.85 for females and F=1 for males

9. * ECOG PS 0-1 within 28 days of randomisation.

10. * Postmenopausal or evidence of non childbearing status for women of childbearing potential: negative urine or serum pregnancy test within 28 days of study treatment and confirmed prior to treatment on Day 1.

    Postmenopausal is defined as:

    - Amenorrheic for 1 year or more following cessation of exogenous hormonal treatments
    - Luteinizing hormone and Follicle stimulating hormone levels in the postmenopausal range for women under 50
    - radiation-induced oophorectomy with last menses >1 year ago
    - chemotherapy-induced menopause with >1 year interval since last menses
    - surgical sterilisation (bilateral oophorectomy or hysterectomy).

11. Women of childbearing potential and their partners, who are sexually active, must agree to the use of 2 highly effective forms of contraception in combination (as described in Appendix E) from the signing of the informed consent, throughout the period of taking study treatment and for at least 1 month after last dose of study drug(s), or they must totally/truly abstain from any form of sexual intercourse (as described in Appendix E).

12. Male patients must use a condom during treatment and for 6 months after the last dose of study drug(s) when having sexual intercourse with a pregnant woman or with a woman of childbearing potential. Female partners of male patients should also use a highly effective form of contraception (see Appendix E for acceptable methods) for 6 months after the last dose of study drug(s) if they are of childbearing potential.

13. Patient is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations.

14. * Patients must have a life expectancy of ≥16 weeks.

3.2 Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

1. * Involvement in the planning and/or conduct of the study (applies to AstraZeneca staff and/or staff at the study site).

2. Cytotoxic chemotherapy, hormonal or non hormonal targeted therapy within 21 days of Cycle 1 Day 1 is not permitted. Palliative radiotherapy must have been completed 21 or more days before Cycle 1 Day 1. The patient can receive a stable dose of bisphosphonates or denosumab for bone metastases, before and during the study as long as these were started at least 5 days prior to study treatment.

3. * More than 2 prior lines of cytotoxic chemotherapy for metastatic disease.

   – Prior treatments with hormonal therapy and non hormonal targeted therapy are allowed and not counted as a prior line of cytotoxic chemotherapy.

   – For the purposes of this protocol, the combination of an aromatase inhibitor and everolimus is not considered cytotoxic chemotherapy.

   – Treatment with biologics will not be considered as prior line of therapy.

4. * Previous randomisation in the present study.

5. * Previous treatment with a PARP inhibitor (including olaparib) or other DDR inhibitor (unless treatment was for less than 3 weeks duration and at least 12 months have elapsed between the last dose and randomisation. Patients that did not tolerate prior treatment are excluded).

6. * Exposure to a small molecule IP within 30 days or 5 half-lives (whichever is longer) prior to randomisation. The minimum washout period for immunotherapy shall be 42 days.

7. * Patients with MDS/AML or with features suggestive of MDS/AML.

8. * Patients with second primary cancer, EXCEPTIONS: adequately treated non melanoma skin cancer, curatively treated in-situ cancer of the cervix, Ductal Carcinoma in Situ (DCIS), stage 1 grade 1 endometrial carcinoma, or other solid tumours curatively treated with no evidence of disease for ≥ 5 years prior to study entry (including lymphomas [without bone marrow involvement]).

9. Mean resting corrected QTc interval using the Fridericia formula (QTcF) >470 msec/female patients and >450 msec for male patients (as calculated per institutional standards) obtained from 3 ECGs performed 2-5 minutes apart at study entry, or congenital long QT syndrome.

   No longer applicable from CSPv6.0 AZD1775 should not be given to patients who have a history of Torsades de pointes unless all risk factors that contributed to Torsades have been corrected. AZD1775 has not been studied in patients with ventricular arrhythmias or recent myocardial infarction.

10. Any of the following cardiac diseases currently or within the last 6 months

    - Unstable angina pectoris
    - Congestive heart failure ≥ Class 2 as defined by the New York Heart Association (see Appendix F)
    - Acute myocardial infarction
    - Conduction abnormality not controlled with pacemaker or medication (patients with a conduction abnormality controlled with pacemaker or medication at the time of screening are eligible)
    - Significant ventricular or supraventricular arrhythmias (patients with chronic rate-controlled atrial fibrillation in the absence of other cardiac abnormalities are eligible)

11. Concomitant use of known strong cytochrome P (CYP) 3A inhibitors (eg. itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (eg. ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil). The required washout period prior to starting study treatment is 2 weeks.

    No longer applicable from CSPv7.0 Patient has had prescription or non-prescription drugs or other products known to be sensitive CYP3A4 substrates or CYP3A4 substrates with a narrow therapeutic index, or to be moderate to strong inhibitors/inducers of CYP3A4 which cannot be discontinued 2 weeks prior to Day 1 of dosing and withheld throughout the study until 2 weeks after the last dose of study drug (see Appendix H).

    No longer applicable from CSPv7.0 Transporter studies (*in vitro*) have shown that AZD1775 is an inhibitor of breast cancer resistance protein (BCRP). Please refer to Appendix H for use with BCRP substrates.

    No longer applicable from CSPv7.0 Patients should stop using herbal medications 7 days prior to first dose of study treatment. Please see Appendix H for further details.

12. Concomitant use of known strong (eg. phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) or moderate CYP3A inducers (eg. bosentan, efavirenz, modafinil). The required washout period prior to starting study treatment is 5 weeks for enzalutamide or phenobarbital and 3 weeks for other agents.

13. Persistent toxicities (≥ CTCAE grade 2) caused by previous cancer therapy, excluding alopecia and CTCAE grade 2 peripheral neuropathy.

14. Major surgery within 2 weeks of starting study treatment: patients must have recovered from any effects of any major surgery.

15. * Immunocompromised patients, eg, patients who are known to be serologically positive for human immunodeficiency virus (HIV).

16. * Patients with known active hepatitis (ie, hepatitis B or C).

17. * Patients considered a poor medical risk due to a serious, uncontrolled medical disorder, non malignant systemic disease or active, uncontrolled infection.

    – Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, extensive interstitial bilateral lung disease on High

Resolution CT scan or any psychiatric disorder that prohibits obtaining informed consent, and any other medical condition that, in the opinion of the Investigator, places the patient at unacceptable risk of toxicity.

18. * Patients with symptomatic uncontrolled brain metastases.

    – A scan to confirm the absence of brain metastases is not required. Patients with spinal cord compression unless considered to have received definitive treatment for this and evidence of clinically stable disease (SD) for 28 days.

    – * Patients with a history of treated central nervous system (CNS) metastases are eligible, provided they meet all of the following criteria: Disease outside the CNS is present. No clinical evidence of progression since completion of CNS-directed therapy. Minimum of 3 weeks between completion of radiotherapy and Cycle 1 Day 1 and recovery from significant (Grade ≥3) acute toxicity with no ongoing requirement for >10 mg of prednisone per day or an equivalent dose of other corticosteroid. If on corticosteroids, the patient should be receiving a stable dose of corticosteroids, started at least 4 weeks prior to treatment.

19. * Patients unable to swallow orally administered medication and patients with gastrointestinal disorders likely to interfere with absorption of the study medication.

20. * Patients with a known hypersensitivity to olaparib, AZD1775, ceralasertib, or any of the excipients of the products.

21. Pregnant or breast feeding women.

Procedures for withdrawal of incorrectly enrolled patients see Section 3.4.

3.3 Patient enrolment and randomisation

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

The Investigator(s) will:

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

2. Assign potential patient a unique enrolment number, beginning with ‘E#’.

3. Determine patient eligibility. See Section 3.1 and 3.2.

If a patient withdraws from participation in the study, then his/her enrolment/randomisation code cannot be reused.

Randomisation codes will be assigned strictly sequentially as patients become eligible for randomisation.

3.3.1 Lynparza HRR Assay

AstraZeneca has partnered with FMI to develop a novel tumour tissue-based companion diagnostic – the Lynparza HRR assay – for the detection of mutations in a panel of 15 HRR genes. FMI will provide the CTA, a novel NGS-based assay that will be performed as a single laboratory testing service using DNA extracted from FFPE tumour tissue. The tumour sample will be tested for qualifying mutation in CCI HRR genes simultaneously: CCI [redacted]. The Lynparza HRR Assay will be based on Foundation Medicine's NGS assay platform (DX1 bait set) for cancer gene profiling. This DX1 bait set covers exons from 310 genes and introns from 35 genes.

All patients must provide a tumour sample that meets the tissue specifications outlined in the laboratory manual, for central tissue testing by FMI using the Lynparza HRR assay. For each patient that passes tissue sample and sequencing quality control, FMI will generate a report specifying the presence or absence of a qualifying mutation in the HRR genes. A qualifying mutation is regarded as deleterious or suspected deleterious if it results in protein truncation (which includes nonsense, frameshift, or consensus splice site mutations), or select missense mutations well known to be deleterious in certain genes (such as *BRCA1, BRCA2*) in ClinVar/BIC databases.

3.4 Procedures for handling incorrectly enrolled or randomised patients

Patients who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Patients who are enrolled, but subsequently found not to meet all the eligibility criteria must not be randomised or initiated on treatment, and must be withdrawn from the study.

Where a patient does not meet all the eligibility criteria but is randomised in error, or incorrectly started on treatment, the Investigator should inform the AstraZeneca study physician immediately, and a discussion should occur between the AstraZeneca study physician and the Investigator regarding whether to discontinue the patient from treatment where required by local law/ local requirements or to continue the study treatment in the best interest of the patient. The AstraZeneca study physician must ensure all decisions are appropriately documented.

3.5 Methods for assigning treatment arms

Eligible patients will be randomised by a ratio 1:1:1 to olaparib monotherapy, ceralasertib+olaparib or AZD1775+olaparib combinations. AZD1775+olaparib arm was closed in April 2019 so randomisation ratio will be 1:1 to olaparib monotherapy or ceralasertib+olaparib. The actual treatment given to individual patients will be determined by

a randomisation scheme that has been loaded into the Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS) database.

The process for randomisation and associated Investigator tasks will be outlined in the IxRS manual.

A blocked randomisation list will be generated at PAREXEL Informatics in accordance with AZ Rand. The randomisation scheme will be stratified based on the

- tumour biomarker strata A, B, C defined in Section 1.4
- patient's prior platinum-based therapy (no / yes)

Randomisation in all centres through IxRS will minimise any imbalance in the total number of patients assigned to each treatment arm. The randomisation list will be loaded into the Interactive Response Technology (IRT) system.

Patient eligibility will be established before treatment randomisation. Once the eligibility of a patient has been confirmed, the Investigator (or nominated assistant) should contact the IRT system for allocation of randomised study treatment. The IRT system will inform the Investigator of the Kit identification (ID) number to be allocated to the patient at the randomisation visit. The Investigator will call/log in to the IRT system for each subsequent dispensing visit for assignment of a new Kit ID number. The Kit ID number dispensed at each visit will correspond to the study treatment to which the patient was originally randomised.

It is recommended that patients commence study treatment as soon as possible after randomisation, and ideally within 3 days.

If a patient discontinues participation in the study, then their enrolment/randomisation code cannot be reused.

Once 75 non HRR*m* patients have been recruited, recruitment into this stratum will be paused while the interim futility analysis is conducted. Similarly, if an interim futility analysis is necessary for the non *BRCAm* HRR*m* stratum, recruitment to stratum B will be paused until the analysis is complete.

3.6 Methods for ensuring blinding

Given the study treatment design (monotherapy and 2 different combination therapies will be employed; monotherapy and 1 combination from April 2019) neither patients nor Investigators will be blinded to study treatment. However, to limit bias on study conduct, data quality, data analyses and data interpretation, appropriate key personnel and certain functions at the Sponsor will remain blinded to treatment allocation until general unblinding of each stratum. Separate unblinded counterparts, e.g. biostatisticians and statistical programmers will do all necessary unblinded work during the course of the study, including the interaction with

the AZ ISRC and URC. Detailed procedures for maintenance of the blind will be described in a Blinding Maintenance Plan.

3.7 Restrictions

3.7.1 Grapefruit juice and Seville oranges

For all patients, it is prohibited to consume grapefruit juice or Seville oranges (including marmalade, juice, etc.) while participating in the study.

3.7.2 Contraception

Women of childbearing potential and their partners, who are sexually active, must agree to the use of TWO highly effective forms of contraception in combination. This should be started from the signing of the informed consent and continue throughout the period of taking study treatment and for at least 1 month after last dose of study drug(s), or they must totally/truly abstain from any form of sexual intercourse.

Male patients must use a condom during treatment and for 6 months after the last dose of study drug(s) when having sexual intercourse with a pregnant woman or with a woman of childbearing potential. Female partners of male patients should also use a highly effective form of contraception if they are of childbearing potential. Male patients should not donate sperm throughout the period of taking study drug(s) and for 6 months following the last dose of study drugs.

Male patients will be advised to arrange for the freezing of sperm samples prior to the start of the study should they wish to father children while on the study or during the 6 months after stopping study treatment.

For details of acceptable methods of contraception refer to Appendix E Acceptable Birth Control Methods.

3.7.3 Sun Exposure

Precautions are advised as a lifestyle recommendation when outside in the sun e.g. limiting the duration of sun exposure, wearing protective clothing (hat and sunglasses) and sunscreen.

3.8 Discontinuation of IP

Patients may be discontinued from IP in the following situations:

- Patient decision. The patient is free, at any time, to discontinue treatment, without prejudice to further treatment.
- AE
- Severe non compliance with the Clinical Study Protocol
- Bone marrow findings consistent with MDS/AML

- Objective progression (based on Investigator assessment) according to RECIST 1.1 criteria (unless in the Investigator's opinion the patient is benefiting from the treatment and does not meet any other discontinuation criteria as outlined in Section 3.9 and Section 3.10).

- Development of any study specific criteria for discontinuation (see Section 3.9 and Section 3.10)

- Unacceptable toxicity (patients can temporarily discontinue IP due to toxicity; IP can be re-started provided the disease has not progressed since discontinuation)

- A positive pregnancy test

3.8.1 Procedures for discontinuation of a patient from IP

At any time, patients are free to discontinue IP or withdraw from the study (ie, IP and assessments – see Section 3.9), without prejudice to further treatment. A patient that decides to discontinue IP will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by an Investigator(s). Adverse events will be followed up (See Section 6); CCI [redacted] (eg, for CCI [redacted]) and all study drugs should be returned by the patient.

By discontinuing from study treatment, the patient is not withdrawing from the study. Patients should be followed for progression (if discontinuation in the absence of progression) and OS following treatment discontinuation as per the protocol schedule.

A patient can discontinue one of the combination drugs for up to 28 days. However, if they need to discontinue one of the combination drugs permanently, they will have to discontinue both combination drugs permanently. Following the ISRC meeting on 17 April 2019 a recommendation was made to close the AZD1775+olaparib treatment arm across all biomarker strata and that patients currently receiving treatment with AZD1775+olaparib treatment be offered the opportunity to continue treatment of olaparib monotherapy at the approved dose (300 mg bd). Any patient discontinuing IP should be seen at 30 days post discontinuation for the evaluations outlined in the study schedule. The patient's tumour status should be assessed clinically and, if appropriate, disease progression should be confirmed by radiological assessment. After discontinuation of study medication, the Principal Investigator (PI)/Sub-Investigator will perform the best possible observation(s), test(s) and evaluation(s) as well as give appropriate medication and all possible measures for the safety of the patient. In addition, they will record on the electronic Case Report Form (eCRF) the date of discontinuation, the reasons, manifestation and treatment at the time of discontinuation. If patients discontinue study treatment, the Study Monitor must be informed immediately. Patients will be required to attend the treatment discontinuation visit. The patient should return all study medication.

Any AEs that are unresolved at the patient's last AE assessment in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the

CRF. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary. Patients should be seen at least 30 days after discontinuing study medication to collect and/or complete AE information. For guidance on reporting AEs after the 30-day follow up period see Section 6.3.1.1.

Any patient who has not yet shown objective radiological disease progression at withdrawal from IP should continue to be followed as per RECIST 1.1.

All patients must be followed for survival, up to the final OS analysis (i.e. when OS data for the ceralasertib+olaparib vs. olaparib monotherapy pairwise comparison is approximately 70% mature).

If a patient is withdrawn from study, see Section 3.9.

3.9 Criteria for withdrawal from the study

Reasons for withdrawal from the study:

- Voluntary withdrawal by the patient who is at any time free to discontinue their participation in the study, without prejudice to further treatment.
- Incorrectly enrolled patients i.e. the patient does not meet the required inclusion/exclusion criteria for the study. If the patient has already been treated, the decision to withdraw will be made in the best interest of the patient by the Investigator and sponsor, in accordance with local law/ local requirements.
- Patient lost to follow-up.
- Death.

3.9.1 Screen failures

Screening failures are patients who do not fulfil the eligibility criteria for the study, and therefore must not be randomised. These patients should have the reason for study withdrawal recorded as ‘Screen failure’(the potential patient who does not meet one or more criteria required for participation in a study, this reason for study withdrawal is only valid for not randomised patients). ‘Failure to meet randomisation criteria’ should be selected for an indication that the patient has been unable to fulfil/satisfy the criteria required for assignment into a randomised arm.

3.9.2 Withdrawal of the informed consent

Patients are free to withdraw from the study at any time (IP and assessments), without prejudice to further treatment.

A patient who withdraws consent will always be asked about the reason(s) and the presence of any AEs. The Investigator will follow up AEs outside of the clinical study.

If a patient withdraws from participation in the study, then his/her enrolment/randomisation code cannot be reused. Withdrawn patients will not be replaced.

If a patient withdraws consent, they will be specifically asked if they are withdrawing consent to:

- further participation in the study including any further follow up (eg, survival calls)
- withdrawal of consent to the use of their study generated data
- withdrawal to the use of any samples (see Section 5.7.4)

The status of ongoing, withdrawn (from the study) and "lost to follow-up" patients at the time of an OS analysis should be obtained by the site personnel by checking the patient notes, hospital records, contacting the patient's general practitioner and checking publicly available death registries. In the event that the patient has actively withdrawn consent to the processing of their personal data, the vital status of the patient can be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws.

3.10 Discontinuation of the study

The study may be stopped if, in the judgment of AstraZeneca, study patients are placed at undue risk because of clinically significant findings that:

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

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

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

4. STUDY PLAN AND TIMING OF PROCEDURES

The scheduled Screening Part 1 and Screening Part 2 assessments are summarized in Table 2 and Table 3, respectively. The scheduled assessments for on-study treatment and study discontinuation are summarized in Table 4 for the olaparib monotherapy arm and the ceralasertib+olaparib arm and in Table 5 for the AZD1775+olaparib arm. Patients on treatment in April 2019 when the AZD1775+olaparib arm was closed will be offered the opportunity to continue treatment of olaparib monotherapy at their next treatment cycle at the approved dose (300 mg bd) and should follow Table 5 continuing treatment on a 21-day cycle.

Table 2 Study schedule – Screening Part 1

Day	Up to Day -28
Informed consent	X
Demographics	X
Medical and surgical history[a]	X
Inclusion criteria # 1, 2, 4, 5, 9, 10, 14 (see Section 3.1)	X
Exclusion criteria # 1, 3, 4, 5, 6, 7, 8, 15, 16, 17, 18, 19, 20 (see Section 3.2)	X
ECOG PS (0-1)	X
Pregnancy test[b]	X
FFPE tumour tissue block or sections for FMI Lynparza HRR assay[c]	X

[a] This should include any previous cancer therapies (including radiotherapy an response to current chemotherapy regimen) as well as any history of blood transfusion within 120 days from start of study treatment, with reasons (eg, bleeding or myelosuppression).

[b] Women of child-bearing potential must have a negative urine or serum pregnancy to be eligible for screening. If results are positive, the patient is ineligible for randomisation in the study.

[c] FFPE tumour tissue blocks are required, but if not available, tissue sections are accepted. At least twenty (20) (thirty [30] preferable) unstained sections without cover slips must be submitted to ensure sufficient material for the prospective Lynparza HRR testing to determine study eligibility. Patients must have a confirmed qualifying HRR mutation status to be eligible for the study. Patients with known HRR status and with documented confirmation of the qualifying mutation may enrol (see Section 5.7).

Table 3 Study schedule – Screening Part 2 (Visit 1)

Day	-28 to 0
Informed consent	X
Demographics	X
Medical and surgical history[a]	X
Inclusion/exclusion criteria	X
ECOG PS (0-1)	X
Vital signs (includes BP, pulse and temperature)	X
Haematology/clinical chemistry/coagulation[b]	X
Urinalysis[c]	X
Pregnancy test[d]	X
Physical examination including weight[e]	X
Tumour assessment (RECIST 1.1)[f]	X
ECG[g]	X
AEs (from time of consent)[h]	X
Concomitant medications including blood transfusions	X
CCI	X
CCI	X
Blood for circulating tumour cells	X
Blood sampling for CCI analysis[i]	X

[a] This should include any previous cancer therapies (including radiotherapy an response to current chemotherapy regimen) as well as any history of blood transfusion within 120 days from start of study treatment, with reasons (eg, bleeding or myelosuppression).

[b] Coagulation test should be performed at screening and sequentially if clinically indicated. For a list of all required laboratory tests please refer to Section 5.2.1.

[c] Urinalysis should be performed at screening. After screening, urinalysis will only be required if clinically indicated.

[d] Women of child-bearing potential must have a negative urine or serum pregnancy test within 28 days prior to starting treatment and a confirmatory test before treatment on Day 1. If results are positive, the patient is ineligible/must be discontinued from the study.

[e] Physical examination should be done as per schedule but does not need to be recorded in the eCRF after the baseline assessment. Any clinically significant changes not unequivocally related to disease progression should be recorded as AEs.

[f] Baseline RECIST 1.1 assessments will be performed using CT scans of the chest, abdomen and pelvis (or MRI where CT is contraindicated) and should be performed no more than 28 days before the start of study treatment and as close as possible to the start of study treatment and prior to randomisation.
Brain CT scan/MRI at baseline should be done for patients with known history of brain metastatic disease.

[g] ECGs are required within 7 days prior to starting study treatment. ECGs should be performed in triplicate.

[h] When an AE for nausea and vomiting occurs, an additional eCRF page will require completion.

[i] Blood samples for CCI analysis (eg, CCI) to be taken during screening.

PBMC=peripheral blood mononuclear cell

Table 4 Study schedule - on study treatment and discontinuation: olaparib monotherapy arm and ceralasertib+olaparib arm

Following the data cut off for the final analysis for PFS for a given stratum, data collection in the eCRF for that stratum will be reduced. It is recommended that the study schedule is followed as outlined below however data entry will be restricted to IP dispensation and accountability, safety laboratory assessments, pregnancy test, AEs and SAEs (see Table 6 for data collection requirement and section 9.3). Following the final analysis for PFS (primary) data cut off for a given stratum exploratory sample collection will stop for that stratum with the exception of the required blood sample for CCI analysis at the time of progression. The tumour biopsy (optional) at the time of progression should also be collected.

Visit Name	**On treatment Cycle 1**			**Subsequent on treatment visits (every 28 days)***	**Study treatment discontinued**	**Follow-up 30 days after last dose of study medication**	**Survival follow-up**
Visit Number	**2**	**3**	**4**	**Visit No. 5 onwards**			
Day	**1**	**7**	**15**	**Cycle X, Day 1[m]**			**Every 8 weeks**
Visit Window			**±3d**	**±3d**	**±7d**	**+7d**	**±7d**
Randomisation[a]	X						
ECOG PS	X			X	X		
Vital signs (includes BP, pulse and temperature)	X[b]			X	X	X	
Haematology/clinical chemistry[c]	X[b]	X	X	X	X	X	
Physical examination and weight[d]	X			X	X	X	
Tumour assessment (RECIST 1.1)[e]				X	X		
ECG[f]	X[f]	X	X	X[f]	X	X	

Visit Name	**On treatment Cycle 1**			**Subsequent on treatment visits (every 28 days)***	**Study treatment discontinued**	**Follow-up 30 days after last dose of study medication**	**Survival follow-up**
Visit Number	**2**	**3**	**4**	**Visit No. 5 onwards**			
Day	**1**	**7**	**15**	**Cycle X, Day 1[m]**			**Every 8 weeks**
Visit Window			**±3d**	**±3d**	**±7d**	**+7d**	**±7d**
Pregnancy test[g]	X			X		X	
Adverse events[h]	X	X	X	X	X	X	
Concomitant medications including blood transfusions	X	X	X	X	X	X	
Anti-cancer therapies							X
CCI	X			X	X		
Optional tumour biopsy at progression					X[j] (Progression only)		
Blood sample for PK analysis[k]	X	X					
CCI	X	X	X	X (Cycle 2only)	X (Progression only)		
Blood for circulating tumour cells	X			X (Cycle 2 only)	X (Progression only)		

Visit Name	**On treatment Cycle 1**			**Subsequent on treatment visits (every 28 days)***	**Study treatment discontinued**	**Follow-up 30 days after last dose of study medication**	**Survival follow-up**
Visit Number	**2**	**3**	**4**	**Visit No. 5 onwards**			
Day	**1**	**7**	**15**	**Cycle X, Day 1[m]**			**Every 8 weeks**
Visit Window			**±3d**	**±3d**	**±7d**	**+7d**	**±7d**
Blood sample for CCI analysis	X			X	X (Progression only)		
Pharmacogenetic sample[l]	X						
Olaparib dosing	← Continuous twice daily dosing →						
Ceralasertib dosing	← Dosing on Days 1-7 only →						
Medication dispensed/returned/medication accountability	X			X	X		
Survival							X

[a] Treatment allocation will be randomised. It is recommended that patients commence study treatment as soon as possible after randomisation, and ideally within 3 days.

[b] If assessment done within 7 days before starting study treatment, does not have to be repeated on Day 1 of study treatment unless the Investigator believes results have changed significantly.

[c] Safety blood samples do not need to be repeated on Day 1 of study treatment if assessed at least 3 weeks after the last dose of chemotherapy but within 7 days before starting study treatment, unless the Investigator believes that it is likely to have changed significantly. Coagulation test should be performed if clinically indicated. Safety blood tests must be reviewed prior to dose administration. For a list of all required laboratory tests please refer to Section 5.2.1.

[d] Physical examination should be done as per schedule but does not need to be recorded in the eCRF after the baseline assessment (except for weight which should be collected at each visit). Any clinically significant changes not unequivocally related to disease progression should be recorded as AEs.

[e] RECIST 1.1 follow-up assessments will be performed every 8 weeks (±1 week) for the first 72 weeks, then every 12 weeks (±1 week) after randomisation until objective disease progression as defined by RECIST 1.1, irrespective of treatment decisions. Any patient who has not yet shown objective radiological disease progression at withdrawal from IP should continue to be followed as per RECIST 1.1. Follow-up assessments will include CT assessments of chest, abdomen and pelvis (or MRI where CT is contraindicated) for all patients. Any other sites at which new disease is suspected should also be appropriately imaged. If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits.

[f] ECG assessment to be done on Day 1 of every cycle, within 1-2 hours prior to dosing. An additional baseline assessment will be conducted on Day 1, Cycle 1.

[g] Pregnancy tests using blood or urine samples will be performed for women of childbearing potential within 28 days prior to the start of study treatment, on Day 1 of the study prior to commencing treatment, on Day 1 of each subsequent treatment cycle and at the follow-up visit 30 days after last dose of study medication. If results are positive, the patient must be discontinued from the study treatment immediately. Tests will be performed by the hospital's local laboratory.

[h] When an AE for nausea and vomiting occurs, an additional eCRF will require completion. All ongoing AEs/SAEs and any new AEs/SAEs identified during the 30 calendar day's follow-up period after last dose of study medication must be followed to resolution.

[i] To be completed every 8 weeks (+/- 1 week) until discontinuation of study treatment. Following the data cut off of for the final analysis for PFS patients will no longer be required to complete the CCI .

[j] Only at progression.

[k] A common PK time window will be used for olaparib and ceralasertib in all patients: Cycle 1 Day 1: 2 hours (±1 hour), 4.5 hours (±1.5 hour) and 9 hours (±3 hours), Cycle 1 Day 7: pre-dose, 0.5hour (±0.5 hour), 2 hours (±1 hour), 4.5 hours (±1.5 hours) and 9 hours (±3 hour).

[l] The pharmacogenetic blood sample can be obtained either at the first treatment visit or after randomisation

[m] If a patient has experienced a Grade 3/4 neutropenia, G4 thrombocytopenia, or a dose interruption due to haematological toxicity in a prior cycle, unscheduled Day 8 and Day 15 complete blood counts are required in subsequent treatment cycles. If no further events are experienced in the subsequent 3 consecutive cycles, then the Day 15 CBC visit can be stopped.

* Please note that the cycle length for olaparib monotherapy and ceralasertib+olaparib treatment arms will be 28 days.

PBMC=peripheral blood mononuclear cell

Table 5 AZD1775+Olaparib Schedule of Assessments (applies to Patients Randomised to this Treatment Arm who, after April 2019, continue on Olaparib monotherapy)

Following the final analysis for PFS for a given stratum, data collection in the eCRF for that stratum will be reduced. It is recommended that the study schedule is followed as outlined below however data entry will be restricted to IP dispensation and accountability, safety laboratory assessments, pregnancy test, AEs and SAEs (see Table 6 for data collection requirement and section 9.3). Following the data cut off exploratory sample collection will stop with the exception of the required blood sample for CCI analysis at the time of progression. The tumour biopsy (optional) at the time of progression should also be collected.

Visit Name	On treatment Cycle 1				On treatment Cycle 2			Subsequent on treatment visits (every 21 days)*	Scan Visit (every 8 weeks[e])	Study treatment discontinued	Follow-up 30 days after last dose of study medication	Survival follow-up
Visit Number	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**Visit No. 9 onwards**				
Day	**1**	**8**	**10**	**15**	**1**	**8**	**15**	**Cycle X, Day 1[o]**	**Scan Day[n]**			**Every 8 weeks**
Visit Window				**±3d**	**±3d**			**±3d**	**±7d**	**±7d**	**+7d**	**±7d**
Randomisation[a]	X											
ECOG PS	X				X			X		X		
Vital signs (includes BP, pulse and temperature)	X[b]	X		X	X	X	X	X		X	X	
Haematology/clinical chemistry[c]	X[b]	X	X	X	X	X	X	X		X	X	
Physical examination and weight[d]	X				X			X		X	X	
Tumour assessment (RECIST 1.1)[e]									X	X		

Visit Name	On treatment Cycle 1				On treatment Cycle 2			Subsequent on treatment visits (every 21 days)*	Scan Visit (every 8 weeks[e])	Study treatment discontinued	Follow-up 30 days after last dose of study medication	Survival follow-up
Visit Number	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**Visit No. 9 onwards**				
Day	**1**	**8**	**10**	**15**	**1**	**8**	**15**	**Cycle X, Day 1[o]**	**Scan Day[n]**			**Every 8 weeks**
Visit Window				**±3d**	**±3d**			**±3d**	**±7d**	**±7d**	**+7d**	**±7d**
ECG[f]	X[f]		X	X	X[f]			X[f]		X	X	
Pregnancy test[g]	X				X			X			X	
AEs[h]	X	X	X	X	X	X	X	X		X	X	
Concomitant medications including blood transfusions	X		X	X	X			X		X	X	
Anti-cancer therapies												X
[redacted]	X								X	X		
Optional tumour biopsy at progression										X[j] (Progression only)		
Blood sample for PK analysis[k]	X		X									
[redacted]	X		X	X	X					X (Progression only)		

Visit Name	On treatment Cycle 1				On treatment Cycle 2			Subsequent on treatment visits (every 21 days)*	Scan Visit (every 8 weeks[e])	Study treatment discontinued	Follow-up 30 days after last dose of study medication	Survival follow-up
Visit Number	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**Visit No. 9 onwards**				
Day	**1**	**8**	**10**	**15**	**1**	**8**	**15**	**Cycle X, Day 1[o]**	**Scan Day[n]**			**Every 8 weeks**
Visit Window				**±3d**	**±3d**			**±3d**	**±7d**	**±7d**	**+7d**	**±7d**
Blood for circulating tumour cells	X				X					X (Progression only)		
Blood sample for CCI analysis[m]	X				X			X	X	X (Progression only)		
Pharmacogenetic sample[p]	X											
Olaparib dosing**								← Continuous twice daily dosing →				
AZD1775 dosing[l]**								← Dosing on Days 1-3 and 8-10 →				
Medication dispensed/returned/medication accountability	X							X		X		
Survival												X

[a] Treatment allocation will be randomised. It is recommended that patients commence study treatment as soon as possible after randomisation, and ideally within 3 days.

[b] If assessment done within 7 days before starting study treatment, does not have to be repeated on Day 1 of study treatment unless the Investigator believes results have changed significantly.

[c] Safety blood samples do not need to be repeated on Day 1 of study treatment if assessed at least 3 weeks after the last dose of chemotherapy but within 7 days before starting study treatment, unless the Investigator believes that it is likely to have changed significantly. Coagulation test should be performed if clinically indicated. Safety blood tests must be reviewed prior to dose administration. For a list of all required laboratory tests please refer to Section 5.2.1. The patient should only proceed with dosing with AZD1775 on Day 1 and Day 8 if the haematology parameters meet the dosing criteria.

[d] Physical examination should be done as per schedule but does not need to be recorded in the eCRF after the baseline assessment (except for weight which should be collected at each visit). Any clinically significant changes not unequivocally related to disease progression should be recorded as AEs.

[e] RECIST 1.1 follow-up assessments will be performed every 8 weeks (±1 week) for the first 72 weeks, then every 12 weeks (±1 week) after randomisation until objective disease progression as defined by RECIST 1.1, irrespective of treatment decisions. Any patient who has not yet shown objective radiological disease progression at withdrawal from IP should continue to be followed as per RECIST 1.1. Follow-up assessments will include CT assessments of chest, abdomen and pelvis (or MRI where CT is contraindicated) for all patients. Any other sites at which new disease is suspected should also be appropriately imaged. If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits.

[f] All ECGs to be done in triplicate. Assessment on Day 1 of every cycle to be taken 1-2 hours prior to dosing. An additional baseline assessment will be conducted on Day 1, Cycle 1. **From April 2019 triplicate ECG no longer applies to patients who have discontinued AZD1775 but single ECGs should be taken at the stated timepoints.**

[g] Pregnancy tests using blood or urine samples will be performed for women of childbearing potential within 28 days prior to the start of study treatment, on Day 1 of the study prior to commencing treatment, on Day 1 of each subsequent treatment cycle and at the follow-up visit 30 days after last dose of study medication. If results are positive, the patient must be discontinued from the study treatment immediately. Tests will be performed by the hospital's local laboratory.

[h] When an AE for nausea and vomiting occurs, an additional eCRF will require completion. All ongoing AEs/SAEs and any new AEs/SAEs identified during the 30 calendar day's follow-up period after last dose of study medication must be followed to resolution.

[i] To be completed every 8 weeks (± 1 week) until discontinuation of study treatment. Following the data cut off for the final analysis for PFS for a given stratum patients will no longer be required to complete the CCI .

[j] Only at progression.

[k] A common PK time window will be used for olaparib and AZD1775 in all patients: Cycle 1 Day 1: 1-3 hours, 3-6 hours and 6-12 hours; Cycle 1 Day 10: pre-dose, 0.5-1 hour, 1-3 hours, 3-6 hours and 6-12 hours. **Not applicable following CSPv6.0**

[l] All patients must receive a 5-HT3 antagonist, ondansetron (Zofran) 8 mg PO or granisetron (Kytril) 1 mg orally prior to each dose of AZD1775. Additional doses of 5-HT3 antagonist may be used if needed. In addition, dexamethasone 4 mg orally will be given with each AZD1775 dose as a minimum on the first day of dosing AZD1775 of every 3 days dosing period, unless contraindicated or not well-tolerated. Dexamethasone may be continued on further days of dosing, potentially at a lower dose. Dexamethasone or the 5-HT3 antagonist may be given by IV. Promethazine (Phenergan), prochlorperazine (Compazine), and benzodiazepine may still be used as additional adjunctive treatments during AZD1775 therapy**. Please note: aprepitant [Emend] and fosaprepitant are not permitted due to known DDIs**- N**o longer applicable following CSPV6.0, provided there has been a minimum washout period of 10 days since the final dose of AZD1775.** Patients should be strongly encouraged to maintain liberal oral fluid intake.

[m] CCI CCI sample should be taken at same visit as scan, if possible. If a CCI sample was taken at a scan visit not coinciding with the CxD1 visit a sample at the CxD1 visit is not required

[n] Scan visit may be tied in with CxD1 visit, using ±7d window, if appropriate

[o] Unscheduled D8 and D15 visits with complete blood counts should be done from C3 onwards if Grade 3/4 neutropenia, G4 thrombocytopenia or a dose interruption due to haematological toxicity was experienced in a prior cycle. If no further events are experienced in the subsequent 3 consecutive cycles, then the Day 15 CBC visit can be stopped. **No longer applicable following CSPv6.0.**

[p] The pharmacogenetic blood sample can be obtained either at the first treatment visit or after randomisation

* Please note that cycle length for AZD1775+olaparib treatment arm is 21 days.

** Please note that for patients on the AZD1775+olaparib treatment arm, the continuous olaparib dose will be 200 mg bd. After April 2019, all patients randomised to this treatment arm discontinued AZD1775 and were offered the opportunity to continue olaparib monotherapy at 300 mg bd on a 21-day cycle starting at the patient's next treatment cycle to ensure a minimum 10 day wash out period from AZD1775 to olaparib monotherapy 300 mg bd dosing to avoid DDI.

PBMC=peripheral blood mononuclear cell

Table 6 eCRF data entry for patients on study treatment following the data cut off for the final analysis for PFS: olaparib monotherapy arm, ceralasertib+olaparib arm and AZD1775+olaparib arm

Following the final analysis for PFS for a given stratum, data collection in the eCRF will be reduced. It is recommended that the study schedule is followed as per Table 4 and Table 5, however data entry will be restricted to IP dispensation and accountability, safety laboratory assessments, pregnancy test, AEs and SAEs (see Table 6 for data collection requirement and section 9.3). Following the data cut off exploratory sample collection will stop with the exception of a blood sample for CCI analysis and a tumour biopsy (optional) at the time of progression.

Visit Name	**Subsequent on treatment visits (every 28 days)***	**Study treatment discontinued**	**Follow-up 30 days after last dose of study medication**	**Survival follow-up**
Visit Number	**Visit No. 5 onwards**			
Day	**Cycle X, Day 1**			**Every 8 weeks**
Visit Window	**±3d**	**±7d**	**+7d**	**±7d**
Haematology/clinical chemistry[a]	X	X	X	
Pregnancy test[b]	X		X	
Adverse events[c]	X	X	X	
Anti-cancer therapies				X
Olaparib dosing	Continuous twice daily dosing			
Ceralasertib dosing	← Dosing on Days 1-7 only →			
Medication dispensed/returned/medication accountability	X	X		
Survival				X
Optional tumour biopsy at progression[d]		X (Progression only)		

Visit Name	**Subsequent on treatment visits (every 28 days)***	**Study treatment discontinued**	**Follow-up 30 days after last dose of study medication**	**Survival follow-up**
Visit Number	**Visit No. 5 onwards**			
Day	**Cycle X, Day 1**			**Every 8 weeks**
Visit Window	**±3d**	**±7d**	**+7d**	**±7d**
Blood sample for CCI analysis[d]		X (Progression only)		

[a] Safety blood tests must be reviewed prior to dose administration. For a list of all required laboratory tests please refer to Section 5.2.1.

[b] Pregnancy tests using blood or urine samples will be performed for women of childbearing potential within 28 days prior to the start of study treatment, on Day 1 of the study prior to commencing treatment, on Day 1 of each subsequent treatment cycle and at the follow-up visit 30 days after last dose of study medication. If results are positive, the patient must be discontinued from the study treatment immediately. Tests will be performed by the hospital's local laboratory.

[c] When an AE for nausea and vomiting occurs, an additional eCRF will require completion. All ongoing AEs/SAEs and any new AEs/SAEs identified during the 30 calendar day's follow-up period after last dose of study medication must be followed to resolution.

[d] Following the final analysis for PFS for a given stratum the only exploratory samples for that stratum that need to be taken are the required blood sample for CCI analysis at the time of progression and the optional tumour biopsy at the time of progression.

4.1 Screening/Enrolment period

Procedures will be performed according to the study plan (see Table 2 and Table 3).

At screening, consenting patients are assessed to ensure that they meet eligibility criteria. Patients who do not meet these criteria must not be randomised in the study.

All patients will be required to provide consent to supply a suitable FFPE prepared tumour sample (that meets the tissue specifications outlined in the Laboratory Manual) for testing on the Lynparza HRR assay for entry into this study. This consent is included in the screening patient informed consent form.

4.2 Treatment period

Procedures during treatment and on study treatment discontinuation will be performed according to Study Plan (see Table 4 and Table 5).

One cycle comprises 28 days for the olaparib monotherapy and ceralasertib+olaparib treatment arms. For the AZD1775+olaparib treatment arm (olaparib monotherapy only following the closure of this treatment arm in April 2019), one cycle comprises 21 days. Unless otherwise specified, procedures should be conducted on the scheduled day (±3 days). This excludes the visits on Day 1 and Day 7 of Cycle 1 for olaparib monotherapy and ceralasertib+olaparib treatment arms and Day 1 and Day 10 of Cycle 1 for the AZD1775+olaparib treatment arm, where all specified procedures should be carried out the same day.

4.3 Follow-up period

Assessments at the end of the treatment period will be conducted 30 days (+7 days) after the last dose of study treatment according to Study Plan (see Table 4 and Table 5).

Survival follow-up will be conducted approximately every 8 weeks (±7 days) after the 30-day follow-up visit according to Study Plan (see Table 4 and Table 5).

5. STUDY ASSESSMENTS

The Clinical Database will be used for data collection and query handling. The Investigator will ensure that data are recorded on the eCRFs as specified in the Clinical Study Protocol and in accordance with the instructions provided.

The Investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement (CSA). The Investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site. For details on keeping source data refer to the CSA (see Section 9.2.1).

5.1 Efficacy assessments

5.1.1 CT and MRI scans; Tumour assessments (RECIST 1.1)

Following the baseline assessment, subsequent tumour assessments according to RECIST 1.1 should be performed every 8 weeks (±1 week) for the first 72 weeks and then every 12 weeks (± 1 week) thereafter, relative to the date of randomisation and irrespective of treatment decisions, up to objective disease progression by RECIST 1.1.

The imaging modalities used for RECIST 1.1 assessment will be CT scans of the chest, abdomen and pelvis (or MRI where CT is contraindicated) with other regions as clinically indicated for the assessment of disease. Brain CT scan/MRI at baseline should be done for patients with known history of brain metastatic disease. Any other sites at which new disease is suspected should also be appropriately imaged. The methods of assessment of tumour burden used at baseline must be used at each subsequent follow-up assessment.

Radiological examinations performed in the conduct of this study should be retained at site as source data.

Coded copies of all scans, regardless of modality, are to be sent to an AstraZeneca appointed CRO for BICR.

All treatment decisions will be based on site assessment of scans. After the primary PFS analysis for each of the strata, central review of scans will no longer be required for that stratum and Investigators will be advised when to stop sending copies of the scans to the CRO conducting the central review. Patients who are determined to have progressed according to RECIST 1.1 criteria by the Investigator will have scans centrally reviewed for confirmation of objective disease progression. If disease progression is not confirmed at central review an additional RECIST 1.1 assessment may be requested preferably at the next scheduled RECIST 1.1 visit, if the central assessment is available in an appropriate timeframe.

It is important to follow the assessment schedule as closely as possible. If scans are performed outside of scheduled visit ± 1 week window interval and the patient has not progressed, every attempt should be made to perform the subsequent scans at their scheduled time points. Patients will be evaluated until objective radiological disease progression by RECIST 1.1 as per the study schedule (see Table 3, and Table 4 and Table 5), and then followed for survival, regardless of whether study treatment is discontinued or delayed and/or protocol violations, unless they withdraw consent.

5.1.2 Tumour evaluation

RECIST 1.1 criteria will be used to assess patient response to treatment by determining PFS times and ORRs as appropriate to study endpoints. The RECIST 1.1 guidelines for measurable, non measurable, target and non target lesions and the objective tumour response criteria (CR, PR, SD or progressive disease [PD]) are presented in Appendix F.

The methods of assessment of tumour burden used at baseline - CT or MRI scans of chest, abdomen, and pelvis (as well as brain CT scan/MRI for patients with known history of brain metastatic disease) must be used at each subsequent follow-up assessment. Any other areas of disease involvement should be additionally imaged based on the signs and symptoms of individual patients.

Following the baseline assessment, efficacy for all patients will be assessed by objective tumour assessments every 8 weeks until Week 72 and every 12 weeks thereafter until objective disease progression as defined by RECIST 1.1. Any other sites at which new disease is suspected should also be appropriately imaged.

If a patient discontinues treatment (and/or receives a subsequent cancer therapy) prior to progression then the patient should still continue to be followed until objective disease progression as defined by RECIST 1.1.

Categorisation of objective tumour response assessment will be based on the RECIST 1.1 criteria of response: CR, PR, SD and PD. Target lesion (TL) progression will be calculated in comparison to when the tumour burden was at a minimum (ie, smallest sum of diameters previously recorded on study). In the absence of progression, tumour response (CR, PR, SD) will be calculated in comparison to the baseline tumour measurements obtained before starting treatment.

Following progression, patients should continue to be followed up for survival approximately every 8 weeks as outlined in the study plan.

It is important to follow the assessment schedule as closely as possible. Please refer to the study plan in Table 3, Table 4 and Table 5.

Following the final PFS analysis data cut off for each stratum (either non HRR*m*, *BRCAm* and/or non *BRCAm* HRR*m*) objective tumour assessments should be performed as per the study schedule (see Table 3, Table 4 and Table 5) for patients continuing on treatment and recorded in the patient notes **but not** recorded in the eCRF.

Central reading of scans

An independent review of all scans used in the assessment of tumours using RECIST 1.1 will be conducted. All imaging assessments including unscheduled visit scans will be collected on an ongoing basis and sent to an AstraZeneca appointed CRO for central analysis up until the data cut off for the final analysis for PFS in an individual stratum. The management of patients will be based solely upon the results of the RECIST 1.1 assessment conducted by the Investigator.

The interim and primary PFS analysis for this study will be based on the BICR of the radiological scans.

5.2 Safety assessments

5.2.1 Laboratory safety assessments

All laboratory assessments described below will be performed at the local laboratories. Blood and urine samples for determination of clinical chemistry, haematology, coagulation, and urinalysis will be taken at the times indicated in the Study Schedule (see Table 3, Table 4 and Table 5).

Following the final PFS analysis data cut off for each stratum (either non HRR*m*, *BRCAm* and/or non *BRCAm* HRR*m*) laboratory assessment samples should be taken as per the study schedule (see Table 3, Table 4 and Table 5) for patients continuing on treatment, recorded both in the patient notes and the eCRF.

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

The clinical chemistry, haematology and urinalysis will be performed at a local laboratory at or near to the Investigator site. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site.

The following laboratory variables will be measured (Table 7):

Table 7 Laboratory safety variables

Haematology/Haemostasis (whole blood)	**Clinical Chemistry (serum or plasma)**
B-Haemoglobin (Hb)	S/P-Creatinine
B-Leukocyte count	S/P-Bilirubin, total
B-Absolute neutrophil count	S/P-Alkaline phosphatase (ALP)
B-Absolute lymphocyte count	S/P-Aspartate transaminase (AST)
B-Platelet count	S/P-Alanine transaminase (ALT)
B-Mean Cell Volume (MCV)	S/P-Albumin
	S/P-Calcium
Urinalysis (dipstick)	S/P-Potassium
U-Hb or Erythrocytes or Blood	S/P-Sodium
U-Protein or Albumin	S/P-Urea or blood urea nitrogen (BUN)
U-Glucose	S/P-Total Protein
	C-reactive protein
Coagulation tests	
Pregnancy tests	

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be retained at centre as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported, see Section 6.3.

In case a patient shows an AST **or** ALT ≥3 x ULN **or** total bilirubin ≥2 x ULN please refer to Appendix D 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions.

5.2.1.1 Coagulation

Coagulation tests should be performed at screening and subsequently if clinically indicated.

- Activated partial thromboplastin time will be performed at screening and sequentially if clinically indicated
- International normalised ratio (INR) will be performed at screening and sequentially if clinically indicated. Patients taking warfarin may participate in this study; however, it is recommended that INR be monitored carefully at least once per week for the first month, then monthly if the INR is stable.
- Each coagulation test result will be recorded on the eCRF.

5.2.1.2 Bone marrow or blood cytogenetic samples

Bone marrow or blood cytogenetic samples may be collected for patients with prolonged haematological toxicities as defined in Section 6.8.1.

Bone marrow analysis should include an aspirate for cellular morphology, cytogenetic analysis and flow cytometry, and a core biopsy for bone marrow cellularity. If it is not possible to conduct cytogenetic analysis or flow cytometry on the bone marrow aspirate, then attempts should be made to carry out the tests on a blood sample. Full reports must be provided by the Investigator for documentation on the Patient Safety database. These data are not required to be entered into the eCRF.

5.2.2 Physical examination

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

Physical examinations will be performed at screening, prior to dosing on Day 1 of each treatment cycle, at study treatment discontinuation, and at the 30-day follow-up (see Table 3, and Table 4 and Table 5).

Following the final PFS analysis data cut off for each stratum (either non HRR*m*, *BRCAm* and/or non *BRCAm* HRR*m*) a complete physical examination should be performed as per the study schedule (see Table 3, Table 4 and Table 5) for patients continuing on treatment and recorded in the patient notes **but not** recorded in the eCRF.

Clinically relevant worsening of physical examination findings will be recorded as AEs for all patients up until the final analysis. For information on recording of AEs see Section 6.3.

5.2.3 ECG

5.2.3.1 Resting 12-lead ECG

Triplicate ECG recordings are required within 7 days prior to starting study treatment (i.e, during screening) in all patients. A single ECG is required at subsequent timepoints for patients in the olaparib monotherapy or ceralasertib+olaparib arms, and triplicate ECGs for patients in the AZD1775+olaparib treatment arm (**from April 2019 triplicate ECG no longer applies to patients who have discontinued AZD1775 but single ECGs should be taken at the stated timepoints)**. ECG recordings are required on Days 1, 7, and 15 of Cycle 1 (Days 1, 10 and 15 of Cycle 1 for the AZD1775+Olaparib arm), on Day 1 of each subsequent cycle (prior to dosing), at study treatment discontinuation, and at the 30-day follow-up (see Table 3, and Table 4 and Table 5).

Following the final analysis for PFS data cut off for a stratum (either non HRR*m*, *BRCAm* or non *BRCAm* HRR*m*), for patients remaining on treatment, ECG recordings should be taken as per the study schedule (see Table 3, Table 4 and Table 5) and recorded in the patient notes **but not** recorded in the eCRF.

Triplicate ECG recordings should be taken within an approximate 5-minute period. Additional ECGs may be taken at any other time the Investigator deems necessary for safety during the administration period. The patients will rest for at least 10 minutes before the start of each recording and they must be in the same supine body position (45 degree flexion in the hip and feet not in contact with the footboard) at the recording time point. The Investigator or designated physician will review the paper copies of each of the timed 12-lead ECGs on each of the study days when they are collected.

ECGs will be recorded at 25 mm/sec. All ECGs should be assessed by the Investigator as to whether they are clinically significantly abnormal / not clinically significantly abnormal. If there is a clinically significant abnormal finding, the Investigator will record it as an AE on the eCRF for all patients up until the final analysis. For information on recording of AEs see Section 6.3. The original ECG traces must be stored in the patient medical record as source data.

Attention should be paid to any detected increases in QTc interval. Patients who develop a single resting value of QTc interval of >450 msec/male and >470 msec/female or a shift from baseline of 60ms should stop taking the study treatment. Dosing can be resumed at a reduced dose after return of the resting QTc interval to pre-treatment status has been confirmed and

correction of possible electrolyte imbalance has been made. Monitoring of QTc, checking and correction of abnormal electrolyte levels and renal function are advised, especially in case of severe/prolonged diarrhoea. If QTc increases markedly from baseline, but stays below the above limits, a cardiologist's advice should be sought. The concomitant use of ondansetron (known to prolong the QTc interval in rare cases, per labelling) should be taken into account when interpreting QTc changes.

5.2.4 Vital signs

Vital signs will be assessed at screening and, if clinically indicated, on Day 1 of each treatment cycle. If the assessments were done within 7 days before starting study treatment, they do not have to be repeated on day 1 of study treatment within the respective treatment cycles unless the Investigator believes results have changed significantly. Vital signs will also be assessed at the 30-day follow-up and at discontinuation (see Table 3, Table 4 and Table 5).

Following the final analysis for PFS data cut off for a stratum (either non HRR*m*, *BRCAm* and/or non *BRCAm* HRR*m*) for patients remaining on treatment vital signs will be assessed as per the study schedule (see Table 3, Table 4 and Table 5) and recorded in the patient notes **but not** recorded in the eCRF.

Weight will be assessed as part of the physical examination (see Section 5.2.2).

Any changes in vital signs should be recorded as an AE, if applicable, for all patients up until the final analysis. For information on how AEs based on changes in vital signs should be recorded and reported, see Section 6.3.

5.2.4.1 Pulse and blood pressure

Blood pressure and pulse will be assessed according to the Study Schedule (see Table 3, and Table 4 and Table 5) and as clinically indicated at any other time.

Blood pressure and pulse rate will be measured preferably using a semi-automatic BP recording device with an appropriate cuff size after 10 minutes rest.

The date of collection and measurement will be recorded on the appropriate eCRF.

Following the final PFS analysis data cut off for a stratum (either non HRR*m*, *BRCAm* and/or non *BRCAm* HRR*m*), for patients remaining on treatment, blood pressure and pulse should be measured as per the study schedule (see Table 3, Table 4 and Table 5) and recorded in the patient notes **but not** recorded in the eCRF.

5.2.4.2 Body temperature

Body temperature will be measured in degrees Celsius according to local practice according to the Study Schedule (see Table 3, Table 4 and Table 5) and as clinically indicated at any other time.

The date of collection and measurement will be recorded on the appropriate eCRF.

Following the final PFS analysis data cut off for a stratum (either non HRR*m*, *BRCAm* and/or non *BRCAm* HRR*m*), for patients remaining on treatment, body temperature should be measured as per the study schedule (see Table 3, Table 4 and Table 5) and recorded in the patient notes **but not** recorded in the eCRF.

5.2.5 Other safety assessments

5.2.5.1 Serum or urine pregnancy test

Pregnancy tests on blood or urine samples will be performed for women of childbearing potential at Screening Part 1 (see Table 2), within 28 days prior to the start of study treatment on Day 1 of the study prior to commencing treatment, at the time points shown in Table 4 and Table 5 during study treatment and at the 30-day follow-up visit. Tests will be performed by the hospital's local laboratory (urine pregnancy dipstick is not permitted). If results are positive the patient is ineligible/must be discontinued from study treatment immediately.

5.3 Other assessments

5.3.1 CCI

5.3.1.1 CCI

In this study, patients will CCI CCI (see Section 5.3.1.2).

CCI

CCI

CCI

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

CCI [redacted]

[redacted]

5.4 Pharmacokinetics

The following PK sampling will be performed on Cycle 1 cross the 3 treatment arms in all patients (see below).

Olaparib arm

	Day 1	Day 7
pre-dose		✓
0.5 hour (±0.5 hour)		✓
2 hours (±1 hour)	✓	✓
4.5 hours (±1.5 hour)	✓	✓
9 hours (±3 hours)	✓	✓

Ceralasertib and olaparib arm

	Day 1	Day 7
pre-dose		✓
0.5 hour (±0.5 hour)		✓
2 hours (±1 hour)	✓	✓
4.5 hours (±1.5 hour)	✓	✓
9 hours (±3 hours)	✓	✓

AZD1775 and olaparib arm - this treatment arm was closed following the ISRC meeting on the 17 April 2019

	Day 1	Day 10
pre-dose		✓
0.5 hour (±0.5 hour)		✓
2 hours (±1 hour)	✓	✓
4.5 hours (±1.5 hour)	✓	✓
9 hours (±3 hours)	✓	✓

For all treatment arms, patients should be instructed to fast and hold their morning dose of AZD1775/olaparib on any day PK sampling is scheduled so it may have timed administration in the clinic. The date and actual time of the PK sample is to be recorded in the medical records and eCRF.

5.4.1 Collection of samples

PK samples are to be taken as blood sample (4mL) for determination of olaparib, ceralasertib and AZD1775 concentrations in plasma. It is essential that PK blood sampling is conducted as close as possible to the planned study timepoints as indicated in Table 4 and Table 5.

5.4.2 Determination of drug concentration

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

5.4.3 Storage and destruction of pharmacokinetic samples

Pharmacokinetic samples will be disposed of after the Bioanalytical Report finalization or six months after issuance of the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses.

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

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

Any residual back-up PK samples may be used for future exploratory biomarker research (in this case, residual back-up PK samples will be shipped to the AZ biobank; see details in the Laboratory Manual).

5.5 Pharmacodynamics

Pharmacodynamics analysis is included as a component of biomarker analysis (see Section 5.7).

5.6 Pharmacogenetics

5.6.1 Collection of genetic samples

If either of the 2 criteria below is met, the patient remains eligible for the study but should not provide a PGx sample:

1. Previous allogenic bone marrow transplant or double umbilical cord blood transplantation.

2. Whole blood transfusions in the last 120 days prior to entry to the study (packed red blood cells and platelet transfusions are acceptable).

The blood sample for genetic research can be obtained at the first treatment visit or after randomisation. Although DNA variants are stable parameter, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an AE, such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn at Visit 1, it may be taken at any visit until the last study visit. Only one sample should be collected per patient for genetics during the study.

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

AstraZeneca or designated organizations will investigate genes and gene expression of relevance to topics such as disease natural history, drug metabolism and response to therapy which may include but will not be limited to genes involved in DNA repair, drug metabolism and immunological fitness, eg, *BRCA1*, *BRCA2*, *CYP2D6*, *HLA-A*, *HLA-B*, *HLA-C*.

5.6.2 Storage and destruction of genetic samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. Samples will be stored for a maximum of 15 years or as per local regulations from the date of the Last Subject Last Visit (LSLV), after which they will be destroyed. DNA is a finite resource that may be used up during analyses. The results of any further analyses will be reported either in the CSR itself or as an addendum, or separately in a scientific report or publication.

No personal details identifying the individual will be available to AstraZeneca or designated organizations working with the DNA.

These tests are not suitable for diagnostic purposes and are exploratory.

5.7 CCI [redacted]

CCI [redacted]

CCI [redacted]

Lynparza HRR gene panel testing of tumour sample

All patients must provide a tumour sample that meets the tissue specifications outlined in Section 3.1 and in the Laboratory Manual for central tissue based HRR gene panel mutation testing by FMI using the Lynparza HRR assay. The tumour sample will be used to test CCI biomarkers simultaneously: CCI [redacted]

Patients who meet all eligibility criteria will be assigned to treatment in the IVRS/IWRS as follows:

Table 8 Stratum assignment based on HRR gene mutation status

HRR gene mutation	Stratum
BRCA1, BRCA2	A
CCI [redacted]	B
No mutation characterised as deleterious detected in any of the HRR genes	C

Collection, Analysis and Reporting of Tumour Samples

Tumour samples will be collected as detailed in the Laboratory Manual and the Pathology and Genomic Testing Manual. Patients must consent to provide a tumour sample for analysis. For patients without a locally confirmed gene mutation samples that meet the minimum tumour content and tissue volume as specified in the Laboratory Manual will be shipped at Screening Part 1 (post confirmation of other [*] marked eligibility criteria, see Section 3.1 and Section 3.2) to FMI (Cambridge MA, USA) to determine HRR status.

If the first sample submitted or testing is inconclusive due to technical test failure, a further sample may be submitted for testing. Submission and testing of additional samples can only be performed if the original testing failed due to technical failure. Please refer to the Laboratory Manual and the Pathology and Genomic Testing Manual for further details regarding retesting procedures.

For each patient that passes tissue sample and sequencing quality control, FMI will generate a report specifying presence or absence of qualifying HRR gene mutations. A patient has a qualifying mutation if any deleterious or suspected deleterious mutation is found in the HRR genes. A mutation is regarded as deleterious if it results in protein truncation (which includes nonsense, frameshift, or consensus splice site mutations), or select missense mutations well known to be deleterious in ClinVar/Breast Cancer Information (BIC) databases in certain genes (*BRCA1*, *BRCA2*). Furthermore, larger scale alterations such as genomic truncating rearrangements or homozygous deletions will also be classified as qualifying. Patients without qualifying HRR gene mutations as determined by the Lynparza HRR assay will be eligible for the study until stratum C is closed for recruitment.

If a patient has a previously confirmed qualifying (deleterious or suspected deleterious) mutation in any of the CCI HRR genes, the patient may meet biomarker testing requirements provided both conditions as described in Section 1.4 are met. An archival tumour sample will be shipped for central assessment of the HRR mutation status after randomisation.

CCI (eg, CCI analysis)

There are two main approaches for the retrieval of tumour material: to obtain contemporary tissue biopsies upon disease progression, or to utilize archival specimens from previous stages of the disease. The former approach requires invasive biopsies, where tissue may be limited in quantity and quality and archival specimens predate progression to advanced breast cancer, and hence, may not reflect tumour evolution and alteration of mutational profile that may have occurred in the intervening timespan. In order to overcome these risks and limitations in the future, exploratory biomarker research will be conducted.

Testing will include (but is not limited to):

- if there is sufficient CCI in plasma for mutation testing
- if CCI in plasma can be used to determine HRR mutation status
- the correlation between tumour and plasma mutation status
- CCI will be collected for future diagnostic development

Patients must provide a blood sample at screening Part 2 (see Table 3). The sample is requested prior to treatment in order to maximize the probability of detecting CCI where the tumour burden is relatively high. Several samples will be taken during treatment and a last sample will be taken at disease progression (see Table 4 and Table 5) up until the final PFS analysis data cut off for each stratum. **Following the final PFS data cut off for each stratum exploratory sample collection CCI , blood for circulating tumour cells, blood sample for CCI) will stop with the exception of the collection of the CCI sample at the time of disease progression (see Table 6).**

Please refer to the Laboratory Manual for further details of biomarker blood sample collection, shipping and storage.

Other exploratory analysis

Patient blood and tumour samples collected during the course of this study may be used for CCI analysis. Such analysis may include, but is not restricted to:

- CCI
- CCI

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

Results of these other exploratory analyses will not be reported in the CSR, but may be added in an appendix to the CSR. No formal statistical analysis is planned.

Future research

Patients may consent to future research where their samples may be analysed following the finalisation of the CSR.

5.7.1 Storage, re-use and destruction of biological samples

Biological samples for future research will be retained at AstraZeneca or its designee for a maximum of 15 years following the finalization of the CSR, after which they will be destroyed. The results of this biomarker research will be reported either in the CSR itself or as an addendum, or separately in a scientific report or publication. The results of this biomarker research may be pooled with biomarker data from other studies with the study drug to generate hypotheses to be tested in future research.

5.7.2 Labelling and shipment of biological samples

The PI ensures that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix B 'International Airline Transportation Association 6.2 Guidance Document'.

Any samples identified as Infectious Category A materials are not shipped and no further samples will be taken from the patient unless agreed with AstraZeneca and appropriate labelling, shipment and containment provisions are approved.

5.7.3 Chain of custody of biological samples

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

The PI at each centre keeps full traceability of collected biological samples from the patients while in storage at the centre until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival, when provided.

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

AstraZeneca keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

Samples retained for further use are registered in the AstraZeneca Biobank system during the entire life cycle.

5.7.4 Withdrawal of Informed Consent for donated biological samples

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

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

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

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

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

6.1 Definition of AEs

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

disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

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

6.1.1 Olaparib, AZD1775 and ceralasertib AEs of Special Interest

Adverse Events of Special Interest (AESIs) are events of scientific and medical interest specific to the further understanding of each agent's safety profile and require close monitoring and rapid communication by the Investigators to AstraZeneca. An AESI may be serious or non serious.

Olaparib AEs of special interest

Adverse Events of Special Interest for olaparib are the Important Potential Risks of MDS/AML, new primary malignancy (other than MDS/AML) and pneumonitis.

ANY event of MDS/AML, new primary malignancy, or pneumonitis should be reported to AstraZeneca Patient Safety whether it is considered a non serious AE (eg non melanoma skin cancer) or SAE, and regardless of Investigator's assessment of causality or knowledge of the treatment arm.

A questionnaire will be sent to any Investigator reporting an AESI, as an aid to provide further detailed information on the event. During the study there may be other events identified as AESIs that require the use of a questionnaire to help characterise the event and gain a better understanding regarding the relationship between the event and study treatment.

AZD1775 AEs of special interest

There are no AESI for AZD1775 which require additional data collection.

Ceralasertib AEs of special interest

There are no AESI for ceralasertib which require additional data collection.

6.2 Definitions of SAE

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation

- Results in persistent or significant disability or incapacity.
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of an SAE, see Appendix A of the Clinical Study Protocol.

6.3 Recording of AEs

6.3.1 Time period for collection of AEs

Adverse events (including SAEs) will be collected from *time of signature of informed consent* throughout the treatment period and including the follow-up period (ie, through the 30-day follow-up visit). All SAEs related to clinical trial procedures are to be recorded from the signing of Screening Part 1 ICFs and all AEs and SAEs are to be recorded from the signing of Screening Part 2 ICFs.

After any interim analysis, any ongoing AEs/SAEs need to be unlocked and followed for resolution.

6.3.1.1 Adverse events after the 30-day follow-up period

For Pharmacovigilance purposes and characterisation, any case of MDS/AML or new primary malignancy occurring after the 30-day follow up period should be reported to AstraZeneca Patient Safety whether it is considered a non serious AE (eg non melanoma skin cancer) or SAE, and regardless of Investigator's assessment of causality or knowledge of the treatment arm. Investigators will be asked during the regular follow up for OS if the patient has developed MDS/AML or a new primary malignancy and prompted to report any such cases.

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

If patients who are gaining clinical benefit are allowed to continue study treatment post data cut off and/or post study completion then all SAEs must continue to be collected and reported to Patient Safety within the usual timeframe.

Otherwise, after study treatment completion (ie, after any scheduled post treatment follow-up period has ended) there is no obligation to actively report information on new AEs or SAEs occurring in former study patients. This includes new AEs/SAEs in patients still being followed up for survival but who have completed the post treatment follow up period (30 days).

6.3.2 Follow-up of unresolved AEs

Any AE that is ongoing at the time of the 30-day follow-up, must be followed up to resolution unless the event is considered by the Investigator to be unlikely to resolve, or the patient is lost to follow up. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

6.3.3 Variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- CTCAE grade and changes in CTCAE
- Whether the AE is serious or not
- Investigator causality rating against the IP (yes or no), comparator/combination drug (yes/no)
- Action taken with regard to IP/comparator/combination drug
- Outcome
- AE caused patient's withdrawal from study (yes or no)

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

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)

- Causality assessment to other medication
- Description of AE.

Severity of AE

For each episode of an AE, all changes to the CTCAE grade attained as well as the highest attained CTC grade should be reported.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE unless it meets the criteria shown in Section 6.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE when it satisfies the criteria shown in Section 6.2.

The grading scales found in the National Cancer Institute (NCI) CTCAE version 4.03 will be utilised for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades the recommendation is that the CTCAE criteria that convert mild, moderate and severe events into CTCAE grades should be used.

A copy of the CTCAE version can be downloaded from the Cancer Therapy Evaluation program website (http://ctep.cancer.gov).

6.3.4 Causality collection

The Investigator will assess causal relationship between IP and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the IP/comparator/combination drug?'

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

A guide to the interpretation of the causality question is found in Appendix A to the Clinical Study Protocol.

6.3.5 Adverse events based on signs and symptoms

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

6.3.6 Adverse events based on examinations and tests

The results from the Clinical Study Protocol mandated laboratory tests and vital signs will be summarised in the CSR. Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs and ECG abnormalities should therefore only be reported as AEs if one of the following is met:

- Any criterion for an SAE is fulfilled
- Causes study treatment discontinuation
- Causes study treatment interruption
- Causes study treatment dose reduction
- The Investigator believes that the abnormality should be reported as an AE

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 Hb value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non mandated parameters should be reported as AE(s).

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

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

6.3.7 Hy's Law

Cases where a patient 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 may need to be reported as SAEs. Please refer to Appendix D for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

6.3.8 Disease progression

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

6.3.9 New cancers

The development of a new primary cancer (including skin cancer) should be regarded as an AE (see Section 6.1.1 Olaparib AEs of special interest). New primary malignancies are those that are not the primary reason for the administration of the study treatment and have developed after the inclusion of the patient into the study. They do not include metastases of the original cancer. Symptoms of metastasis or the metastasis itself should not be reported as an AE/SAE, as they are considered to be disease progression.

6.3.10 Lack of efficacy

When there is deterioration in the cancer, there may be uncertainty as to whether this is lack of efficacy or an AE. In such cases, unless the Sponsor or the reporting physician considers that the study treatment contributed to the deterioration of the condition, or local regulations state to the contrary, the deterioration should be considered to be a lack of efficacy and not an AE.

6.3.11 Deaths

All deaths that occur during the study, or within the protocol defined 30-day follow-up period after the administration of the last dose of study treatment, must be reported as follows:

- Death clearly the result of disease progression should be reported to the study monitor at the next monitoring visit and should be documented in the DEATH eCRF but should not be reported as an SAE.

- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to the study monitor as an SAE within 24 hours (see Section 6.4) for further details. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death. This information can be captured in the death eCRF.

- Deaths with an unknown cause should always be reported as an SAE. A post mortem maybe helpful in the assessment of the cause of death, and, if performed, a copy of the post mortem results should be forwarded to AstraZeneca within the usual timeframes.

6.4 Reporting of SAEs

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

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

The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within**

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

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

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

If the Clinical Database is not available, then the Investigator or other study site staff reports an SAE to the appropriate AstraZeneca representative by telephone.

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

The reference document for definition of expectedness/listedness is the IB for the AstraZeneca drug and the EU Summary of Product Characteristics, USPI or other local label for the active comparator products (including any AstraZeneca comparator).

Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

For all studies except those utilizing medical devices investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure or and will notify the IRB/IEC, if appropriate according to local requirements.

6.5 Overdose

There is currently no specific treatment in the event of overdose with olaparib ceralasertib or AZD1775 and possible symptoms of overdose are not established.

To date, there has been one patient who has experienced an overdose with AZD1775 which was associated with AEs.

Olaparib, ceralasertib, and AZD1775 must only be used in accordance with the dosing recommendations in this protocol. Any dose or frequency of dosing that exceeds the dosing regimen specified in this protocol should be reported as an overdose.

Adverse reactions associated with overdose should be treated symptomatically and should be managed appropriately.

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

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

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with an SAE, the standard reporting timelines apply, see Section 6.4. For other overdoses, reporting must occur within 30 days.

6.6 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- If the pregnancy is discovered before the study patient has received any study drug.

6.6.1 Maternal exposure

If a patient becomes pregnant during the course of the study all IPs should be discontinued immediately.

The outcome of any conception occurring from the date of the first dose of study medication until 1 month after the last dose of study medication must be followed up and documented.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as

SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs from the date of the first dose of study medication until 1 month after the last dose of study medication, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 6.4) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the CRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

6.6.2 Paternal exposure

Male patient should refrain from fathering a child or donating sperm during the study and for 6 months following the last dose.

Pregnancy of the patient's partners is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should if possible be followed up and documented. To capture information about a pregnancy from the partner of a male patient, the male patient's partner consent must be obtained to collect information related to the pregnancy and outcome; the male patient should not be asked to provide this information. The outcome of any conception occurring should be followed up and documented.

The outcome of any conception occurring from the date of the first dose until 3 months *after the last dose* should be followed up and documented.

6.7 Medication Error

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

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

Medication error includes situations where an error:

- occurred.

- was identified and intercepted before the patient received the drug.
- did not occur, but circumstances were recognize that could have led to an error.

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

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

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

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

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

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

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within 1 or 5 calendar days if there is an SAE associated with the medication error (see Section 6.4) and within 30 days for all other medication errors.

6.8 Management of IP related toxicities, Dose reductions

Any toxicity observed during the course of the study could be managed by interruption of the dose of study treatment or dose reductions.

Repeat dose interruptions are allowed as required, for a maximum of 3-4 weeks on each occasion (depending on the toxicity and treatment arm). If study treatment cannot be restarted within the specified period, then the patient must permanently discontinue study treatment. If the interruption is any longer, the study team must be informed.

For olaparib, study treatment can be dose reduced to 250 mg bd as a first step and to 200 mg bd as a second step. If the reduced dose of 200 mg bd is not tolerable, no further dose reduction is allowed and study treatment should be discontinued.

Table 9 Dose reductions for olaparib

Initial Dose	Following re-challenge post interruption: Dose reduction 1	Dose reduction 2
300 mg bd	250 mg bd	200 mg bd

No longer applies from CSPv6.0. For AZD1775, only 1 dose reduction will be allowed. Patients requiring >1 dose reduction will be discontinued from the study drug. Only one dose reduction in olaparib is permitted in the AZD1775+olaparib treatment arm.

Table 10 No longer applies from CSPv6.0 - AZD1775+olaparib dose reduction

Dose Level	AZD1775	olaparib
Initial dose, 21-day cycle	150 mg bd D 1-3 and D 8-10	200mg bd continuous
Dose reduction	* Dose reduce either AZD1775 or olaparib or both	
	125 mg bd D 1-3 and D 8-10	150mg bd continuous

*AZD1775 and olaparib may be reduced in a stepwise manner e.g. first event, dose reduce AZD1775; second event, dose reduce olaparib. If a dose reduction is required for neutropenia, leukopenia or thrombocytopenia, dose reduction of AZD1775 should be implemented first. AZD1775 and olaparib may be dose reduced simultaneously depending on the severity of the event. Dose reductions for anaemia should occur for olaparib first (with consideration to a simultaneous dose reduction in AZD1775 depending on the severity, duration and recurrence of the anaemia).

Once a dose is reduced, re-escalation is not permitted. Due to the recommendation to close the AZD1775+olaparib arm in April 2019 patients continuing treatment on the

AZD1775+olaparib treatment arm should be offered the opportunity to escalate the dose of olaparib to 300 mg bd continuing on a 21-day cycle starting at the patient's next treatment cycle. If a patient has had a dose reduction of olaparib due to toxicity on this treatment combination, the investigator may consider a stepwise increment in the olaparib dose at their discretion, e.g. 200 mg, 250 mg then 300 mg. The visit schedule should be followed as per Table 5 at escalation. For patients continuing on olaparib monotherapy at 300 mg bd please follow the toxicity management guidance as per olaparib monotherapy.

For ceralasertib, study treatment can be dose reduced according to the following dose modification table. A maximum of two dose reduction steps are permitted. If after the second dose reduction treatment is not tolerated, no further dose reduction is allowed and study treatment should be discontinued. Once a dose is reduced, re-escalation is not permitted.

Table 11 Ceralasertib+olaparib dose reduction

Third dose reduction: No further reduction, withdraw patient and treat as clinically indicated.
* Ceralasertib and olaparib may be reduced stepwise within each dose reduction level e.g. dose reduce olaparib first followed by ceralasertib if the adverse event recurs. Dose reductions for anaemia should occur for olaparib first (with consideration to a simultaneous dose reduction in ceralasertib depending on the severity, duration and recurrence of the anaemia). If a dose reduction is required for neutropenia, leukopenia and thrombocytopenia, olaparib and ceralasertib should be dose reduced simultaneously as there is a greater frequency associated with ceralasertib. Once a dose is reduced, re-escalation is not permitted.

6.8.1 Management of haematological toxicity

6.8.1.1 Olaparib monotherapy and ceralasertib combination (includes patients continuing on olaparib monotherapy randomised to the AZD1775+olaparib arm)

Olaparib monotherapy and ceralasertib+olaparib combination: Complete blood counts will be obtained for all patients at Day 1, 7 and 15 in cycle 1, and then at the beginning of each treatment cycle (Day 1). Complete blood counts must be reviewed prior to dose administration. If hematologic toxicity occurs treatment should be modified as below (Table 12 for Day 1 of each cycle and Table 14 observed at any time during the cycle after Day 1)

and ANC and platelets should be monitored weekly (more often as clinically indicated until recovery). For grade 2 and 4 events please also refer to Table 14. If haematologic parameters do not recover within 28 days, the patient should be removed from the study treatment.

Table 12 Day 1 Haematologic dose modifications and management

Treatment day blood counts and toxicity			
ANC		**Platelets**	**Action**
≥1,500/µL	And	≥100,000/µL	No dose modification or interruption
<1,500/µL	Or	<100,000/µL	Delay by 1 week intervals until recovery

Table 13 Management of anaemia

Haemoglobin	**Action to be taken**
Hb <10 *but* ≥8 g/dL (CTCAE Grade 2)	Give appropriate supportive treatment and investigate causality. Investigator judgement to continue study treatment with supportive treatment (eg transfusion) *or* interrupt dose for a maximum of 4 weeks until recovery to grade 1 or better (≥10g/dL). CCI [redacted]
Hb <8 g/dL (CTCAE Grade 3)	Give appropriate supportive treatment (eg, transfusion) and investigate causality. Interrupt study treatment for a maximum of 4 weeks until improved to Hb ≥10 g/dL. CCI [redacted]

Common treatable causes of anaemia (eg, iron, vitamin B12 or folate deficiencies and hypothyroidism) should be investigated and appropriately managed. In some cases management of anaemia may require blood transfusions. For cases where patients develop prolonged haematological toxicity (≥2 week interruption/delay in study treatment due to CTCAE grade 3 or worse anaemia and/or development of blood transfusion dependence), refer to Section 6.8.1.4 for management of this.

6.8.1.2 Olaparib monotherapy and ceralasertib combination: Management of neutropenia, leukopenia and thrombocytopenia (includes patients continuing on olaparib monotherapy randomised to the AZD1775+olaparib arm)

Table 14 provides guidance for hematologic toxicity (neutropenia, leukopenia and thrombocytopenia) observed any time during the study treatment period. **For Day 1 of each cycle please check the required blood counts to commence treatment in Table 12.**

Table 14 Management of neutropenia, leukopenia and thrombocytopenia

Toxicity	Study treatment dose adjustment
CTCAE Grade 1-2	Investigator judgement whether to continue treatment or dose interrupt. If dose interrupted this should be for a maximum of 4 weeks. All patient should have appropriate supportive treatment and causality investigation.
CTCAE Grade 3-4	Dose interruption until recovered to CTCAE grade 1 or better for a maximum of 4 weeks. If repeat CTCAE grade 3-4 occurrence, CCI [redacted] as a second step.

Adverse events of neutropenia and leukopenia should be managed as deemed appropriate by the Investigator with close follow up and interruption of study drug if CTC grade 3 or worse neutropenia occurs.

If a patient has experienced a Grade 3/4 neutropenia, G4 thrombocytopenia, or a dose interruption due to haematological toxicity in a prior cycle, unscheduled Day 8 and Day 15 complete blood counts are required in subsequent treatment cycles. If no further events are experienced in the subsequent 3 consecutive cycles, then the Day 15 CBC visit can be stopped, see Table 4.

Primary prophylaxis with G-CSF is not recommended, however, if a patient develops febrile neutropenia, study treatments should be stopped and appropriate management including G-CSF should be given according to local hospital guidelines. G-CSF should not be used within 24hrs of the last dose prior to dose interruption. Please note that G-CSF should not be used within 24 h of the last dose of study treatment unless absolutely necessary.

Platelet transfusions, if indicated, should be done according to local hospital guidelines.

For cases where patients develop prolonged haematological toxicity (>2 week interruption/delay in study treatment due to CTC grade 3 or worse), refer to Section 6.8.1.4.

6.8.1.3 Not applicable following CSPv6.0 - AZD1775: Dose modifications due to hematologic toxicity

Complete blood counts (CBC) will be obtained for all patients at Day 1, 8 and 15 in cycles 1 and 2 (in addition to the Cycle 1 Day 10 visit). Complete blood counts must be reviewed prior to dose administration.

If treatment is interrupted due to hematologic toxicity, ANC and platelets should be monitored **at least weekly** (or more frequently at the Investigator's discretion) and until blood counts recover to enable AZD1775 dosing. Dosing may then resume according to the dosing guidelines as per Table 15.

If a patient has experienced a Grade 3/4 neutropenia, G4 thrombocytopenia, or a dose interruption due to haematological toxicity in a prior cycle, unscheduled Day 8 and Day 15 complete blood counts are required in subsequent treatment cycles. If no further events are experienced in the subsequent 3 consecutive cycles, then the Day 15 CBC visit can be stopped.

Patients should be managed as medically indicated.

AZD1775 Day 1 and Day 8 dosing criteria: Treatment should not be administered unless the ANC is ≥1.5 x 109/L or 1,500/ µL (Grade 1) and platelets ≥ 100,000/ µL

Table 15 Day 1 (and Day 8 where applicable) Neutrophil and platelet blood counts and study drug action

Neutrophil count	**1st event**	**Action AZD1775**	**2nd event**	**Action AZD1775**
Grade 2 <1.5-1.0 x10^9/L		Hold Resume at 150 mg bd		Hold Resume at 125 mg bd
Grade 3 <1.0-0.5 x10^9/L		Hold Resume at 125 mg bd		Discontinue and follow for disease progression
Grade 3 <1.0-0.5 x10^9/L with documented infection and/or fever		Hold Resume at 125mg bd		Discontinue and follow for disease progression
Grade 4 <0.5 x10^9/L		Hold Resume at 125mg bd		Discontinue and follow for disease progression
Grade 4 Febrile neutropenia or Grade 4 Infection with neutropenia		Discontinue and follow for disease progression		
Platelet count	**1st event**	**Action AZD1775**	**2nd event**	**Action AZD1775**
Grade 2 75,000-50,000/ µL		Hold Resume at 150 mg bd		Hold Resume at 125 mg bd
Grade 3 50,000- 25,000/ µL		Hold Resume at 125 mg bd		Discontinue and follow for disease progression
Grade 4 <25,000/ µL without any evidence of bleeding		Hold Resume at 125 mg bd		Discontinue and follow for disease progression
Thrombocytopenic haemorrhage (gross occult bleeding) associated with platelet count <50,000/ µL		Discontinue and follow for disease progression		

Dose re-escalation is not allowed. If the patient has concurrent neutropenia and thrombocytopenia, please follow the most conservative guidance in Table 15 and discuss with Medical Monitor as needed. GCSF may be used in the event of neutropenia according to institutional standards. Please consider using G-CSF in the event of severe neutropenia or febrile neutropenia.

Table 16 Management of anaemia

Haemoglobin	Action to be taken
Hb <10 but ≥8 g/dL (CTCAE Grade 2)	Give appropriate supportive treatment and investigate causality. Investigator judgement to continue AZD1775/olaparib with supportive treatment (eg transfusion) or interrupt dose for a maximum of 4 weeks. CCI [redacted] efer to Table 9
Hb <8 g/dL	Give appropriate supportive treatment and investigate causality. Interrupt AZD1775/olaparib for a maximum of 4 weeks, until improved to Hb ≥10 g/dL. CCI [redacted]

Common treatable causes of anaemia (eg, iron, vitamin B12 or folate deficiencies and hypothyroidism) should be investigated and appropriately managed. In some cases management of anaemia may require blood transfusions. For cases in which patients develop prolonged haematological toxicity (≥2 weeks interruption/delay in study treatment due to CTCAE grade 3 or worse anaemia and/or development of blood transfusion dependence), refer to Section 6.8.1.4.

Table 17 Neutropenia, infection, febrile neutropenia dose modifications and management

Any day	
Grade 3 neutropenic fever (ANC <1000/µL + Temperature ≥101°F [38.5°C]) or neutropenic infection **Documented infection with Grade 3 neutropenia** (ANC <1000/µL) **Grade 4 neutropenia** (ANC <500/µL >7 days **Grade 4 thrombocytopenia** (platelet count <25,000/µL >7 days)	**Hold dose until recovery.** **Then, upon resuming dosing, reduce AZD1775[a].**
Grade 4 febrile neutropenia or Grade 4 infection with neutropenia (both defined as septic shock) **Thrombocytopenic haemorrhage** (gross occult bleeding) associated with a platelet count <50,000/µL	**Discontinue treatment and follow for disease progression.**

[a] Only 1 dose reduction will be allowed for any patient. Patients requiring an additional dose modification to AZD1775 due to toxicity will discontinue study treatment.

6.8.1.4 Management of prolonged haematological toxicities while on study treatment

If a patient develops prolonged haematological toxicities such as:

- ≥2 week interruption/delay in study treatment due to CTC grade 3 or worse anaemia and/or development of blood transfusion dependence
- ≥2 week interruption/delay in study treatment due to CTC grade 3 or worse neutropenia (ANC < 1 x 10^9/L).
- ≥2 week interruption/delay in study treatment due to CTC grade 3 or worse thrombocytopenia (Platelets < 50 x 10^9/L) and/or development of platelet transfusion dependence.

Check weekly differential blood counts including reticulocytes and peripheral blood smear. If any blood parameters remain clinically abnormal after 4 weeks of dose interruption, the patient should be referred to haematologist for further investigations. Bone marrow analysis and/or blood cytogenetic analysis should be considered at this stage according to standard haematological practice. Study treatment should be discontinued if blood counts do not recover to CTC grade 1 or better within 4 weeks of dose interruption.

Development of a confirmed MDS or other clonal blood disorder should be reported as an SAE and full reports must be provided by the Investigator to AstraZeneca Patient Safety. Study treatment should be discontinued if patient's diagnosis of MDS and/or AML is confirmed.

6.8.2 Management of non haematological toxicity

Acute toxicities in all treatment arms should be managed as medically indicated, with temporary suspension of IP and initiation of supportive care as clinically indicated by the treating physician. Treatment must be interrupted if any NCI-CTCAE Grade 3 or 4 non-hematologic AE occurs which the Investigator considers to be related to the administration of the study treatment(s). Treatment should not be restarted until the toxicity has resolved to Grade ≤ 1. Repeat dose interruptions are permitted, for a maximum of one cycle of treatment. **Any patient who develops a Grade 3 or 4 non-hematologic toxicity that does not resolve to ≤ Grade 1 within this period, should be removed from the study treatment.**

Olaparib

Repeat dose interruptions are allowed as required, for a maximum of 4 weeks on each occasion. If study treatment cannot be restarted within 4 weeks, then the patient must permanently discontinue study treatment. If the interruption is any longer than this the study monitor must be informed. Where toxicity reoccurs following re-challenge with study treatment, and where further dose interruptions are considered inadequate for management of toxicity, then the patient should be considered for dose reduction or must permanently discontinue study treatment.

Olaparib can be dose reduced to 250 mg bd as a first step and to 200 mg bd as a second step. Treatment must be interrupted if any NCI-CTCAE grade 3 or 4 AE occurs which the Investigator considers to be related to administration of study treatment.

AZD1775 - this treatment arm was closed following the ISRC meeting on the 17 April 2019

Substantial acute toxicities should be managed as medically indicated and with temporary suspension of IP, as appropriate. Dose reduction or holds and initiation of supportive care are allowed as clinically indicated by the treating physician.

Dose reduction of AZD1775 should be considered if the toxicity is considered to be related to AZD1775, ie, in monotherapy studies or in combination studies if relationship cannot be wholly attributed to the combination agent (each combination agent should be considered on an individual basis). Dose re-escalation is not permitted.

In general, if a patient experiences a G1/G2 non-haematological toxicity, no dose modification is required (except QTc prolongation, see Table 18 below). If a patient experiences a G3 or G4 toxicity which is not attributable to the disease or disease-related processes under investigation, dosing will be interrupted and/or the dose reduced, and supportive therapy administered as required. Any patient who develops a Grade 3 or 4 non-haematologic toxicity that does not resolve to ≤ Grade 1 within 21 days should be removed from the study treatment unless approved by the Medical Monitor.

Table 18 AZD1775 dose modifications for QTc interval prolongation (No longer applicable following CSPv6.0)

Electrocardiogram QT corrected interval prolonged	
QTc value	**AZD1775**
QTc 450-480 ms (males) or 470-480 (females)	Hold. Once QTc interval has returned to pretreatment status and correction of possible electrolyte imbalance has been made, resume at next lower dose level.
QTc 481-500 ms	Hold. Seek cardiologist advice. Patient may resume with dose reduction if cardiologist agrees.
QTc ≥ 501 ms	Discontinue treatment. Seek cardiologist advice.
Shift from baseline of ≥ 60ms	Discontinue treatment. Seek cardiologist advice.

6.8.2.1 Management of new or worsening pulmonary symptoms

If new or worsening pulmonary symptoms (eg, dyspnoea) or radiological abnormalities occur in the absence of a clear diagnosis, an interruption in study treatment dosing is recommended and further diagnostic workup (including a high resolution CT scan) should be performed to exclude pneumonitis.

Following investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, then study treatment can be restarted, if deemed appropriate by the Investigator. If significant pulmonary abnormalities are identified but pneumonitis cannot be confirmed, these need to be discussed with the Study Physician. If pneumonitis is confirmed, the patient should be discontinued from study treatment and treated appropriately.

6.8.2.2 Management of nausea and vomiting

Olaparib

Events of nausea and vomiting are known to be associated with olaparib treatment. In study D0810C00019 nausea was reported in 71% of the olaparib treated patients and 36% in the placebo treated patients and vomiting was reported in 34% of the olaparib treated patients and 14% in the placebo treated patients. These events are generally mild to moderate (CTCAE grade 1 or 2) severity, intermittent and manageable on continued treatment. The first onset generally occurs in the first month of treatment for nausea and within the first 6 months of treatment for vomiting. For nausea, the incidence generally plateaus at around 9 months, and for vomiting at around 6 to 7 months.

Gastrointestinal AEs including decreased appetite, dyspepsia, nausea, vomiting and diarrhoea (with or without dehydration or serum electrolyte decreases) have been associated with AZD1775. The clinical study protocols for AZD1775 studies, where appropriate, will mandate the use of prophylactic antiemetics and include guidance for the prompt introduction of vigorous anti-diarrhoeal therapy at the first onset. The Investigator must consult the study protocol for specific guidance for management of gastrointestinal toxicities including prophylactic medications. Patients should therefore be closely monitored for signs of gastrointestinal AEs and patient's hydration status, electrolytes, weight and other vital signs should be carefully monitored. Patients will be managed clinically with supportive therapy and dose modification and should be strongly encouraged to maintain liberal oral fluid intake. Aprepitant and fosaprepritant are not permitted as co-medications due to known DDIs with AZD1775.

Antiemetic prophylaxis recommendations should be followed for the AZD1775+olaparib arm. In general, all patients should receive appropriate anti-emetic treatment at the first onset of nausea or vomiting and as required thereafter, in accordance with local treatment practice guidelines. Alternatively, olaparib tablets can be taken with a light meal/snack (ie, 2 pieces of toast or a couple of biscuits).

As per international guidance on anti-emetic use in cancer patients (ESMO, NCCN), generally a single agent antiemetic should be considered eg, dopamine receptor antagonist, antihistamines or dexamethasone.

AZD1775 - this treatment arm was closed following the ISRC meeting on the 17 April 2019

All patients must receive a 5-HT3 antagonist, ondansetron (Zofran) 8 mg PO or granisetron (Kytril) 1 mg PO prior to each dose of AZD1775. Additional doses of 5-HT3 antagonist may be used if needed. In addition, dexamethasone 4 mg PO will be given with each AZD1775 dose as a minimum on the first day of dosing AZD1775 of every 3 days dosing period, unless contraindicated or not well-tolerated. Dexamethasone may be continued on further days of dosing, potentially at a lower dose. Dexamethasone or the 5-HT3 antagonist may be given by IV as needed.

Promethazine (Phenergan), prochlorperazine (Compazine), and benzodiazepine may still be used as additional adjunctive treatments during AZD1775 therapy.

Please note: aprepitant (Emend) and fosaprepitant are not permitted due to known DDIs. N**o longer applicable following CSPV6.0, provided there has been a minimum washout period of 10 days since the final dose of AZD1775.**

Patients should be strongly encouraged to maintain liberal oral fluid intake.

Suitable alternative medications may be used, with adequate justification, in those studies where the use of any of the above medications might interfere with other study procedures or are deemed insufficient.

6.8.2.3 Management of diarrhoea

Due to frequent reports of diarrhoea with AZD1775 administration, vigorous anti-diarrhoeal treatment loperamide (Imodium) is required at the **first** onset of diarrhoea according to American Society of Clinical Oncology (ASCO) guidelines. Oral loperamide (Imodium) 4 mg should be administered at the first onset of diarrhoea and then 2 mg every 2 hours until diarrhoea-free for at least 12 hours. The first dose of loperamide could be lowered to 2 mg if the diarrhoea is recurrent and if, in the opinion of the treating physician, the diarrhoea is not severe.

Patients should be instructed to notify the Investigator or research staff of the occurrence of bloody or black stools, symptoms of dehydration, fever, inability to take liquids by mouth, and inability to control diarrhoea within 24 hours of using loperamide or other prescribed anti-diarrhoeal medications.

If diarrhoea is severe (ie, requiring intravenous [IV] rehydration) and/or associated with fever or severe neutropenia (Grade 3 or 4), broad-spectrum antibiotics must be prescribed. Patients with severe diarrhoea or any diarrhoea associated with severe nausea or vomiting should be hospitalised for IV hydration and correction of electrolyte imbalances.

6.8.2.4 Interruptions for intercurrent non toxicity related events

Study treatment dose interruption for conditions other than toxicity resolution should be kept as short as possible. If a patient cannot restart study treatment within 4 weeks for resolution of intercurrent conditions not related to disease progression or toxicity, the case should be discussed with AstraZeneca Study Physician.

All dose reductions and interruptions (including any missed doses), and the reasons for the reductions/interruptions are to be recorded in the eCRF. Study treatment should be stopped at least 3 days prior to planned surgery. After surgery study treatment can be restarted when the wound has healed. No stoppage of study treatment is required for any needle biopsy procedure.

Study treatment should be discontinued for a minimum of 3 days before a patient undergoes radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.

Because the AEs related to olaparib may include asthenia, fatigue and dizziness, patients should be advised to use caution while driving or using machinery if these symptoms occur.

6.8.3 Management in the event of renal impairment

If subsequent to study entry and while still on study therapy, a patient's estimated CrCl falls below the threshold for study inclusion (≥51 mL/min), retesting should be performed promptly.

A dose reduction is recommended for patients who develop moderate renal impairment (calculated CrCl by Cockcroft-Gault equation of between 31 and 50 mL/min) for any reason during the course of the study: the dose of olaparib should be reduced to 200 mg bd.

Olaparib, AZD1775 and ceralasertib have not been studied in patients with severe renal impairment (CrCl ≤30 mL/min) or end-stage renal disease; if patients develop severe impairment or end stage disease is it recommended that the study treatment be discontinued.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of IP(s)

AstraZeneca's Pharmaceutical Development, R&D Supply Chain will supply olaparib, ceralasertib and AZD1775 to the Investigators. **Following the ISRC meeting on 17 April 2019 and the recommendation to close the AZD1775+olaparib treatment arm across all biomarker strata AZD1775 will not be supplied to sites.**

Investigational product[a]	Dosage form and strength
Olaparib	100 mg film coated tablet
Olaparib	150 mg film coated tablet
Ceralasertib	20 mg, 80 mg, or 100 mg film coated tablet
AZD1775 (not applicable from CSP v6.0)	25 mg, 50 mg, 75 mg, 100 mg, or 200 mg dry-filled capsules

[a] Descriptive information for each agent can be found in the respective IBs

7.2 Dose and treatment regimens

Olaparib

Olaparib tablets will be packed in high-density polyethylene bottles with child-resistant closures and will be available as film coated tablets containing 100 mg or 150 mg of olaparib. Each dosing container will contain sufficient medication for at least 28 days plus coverage. Olaparib will be dispensed to patients on Day 1 of every cycle until the patient completes the study, withdraws from the study or closure of the study. Medication accountability should be completed at Day 1 of each Cycle (Table 4 and Table 5).

In the olaparib monotherapy treatment arm as well as in the ceralasertib+olaparib treatment arm, patients will be administered olaparib bd at 300 mg continually. Two (2) 150 mg olaparib tablets should be taken at the same time each day, approximately 12 hours apart with one glass of water (approximately 250 mL). In the AZD1775+olaparib treatment arm, patients will be given olaparib 200 mg bd (2 x 100 mg tablets twice a day). Following the ISRC meeting on 17 April 2019 a recommendation was made to close the AZD1775+olaparib treatment arm across all biomarker strata and that patients currently receiving treatment with AZD177+olaparib treatment be offered the opportunity to continue treatment of olaparib monotherapy at the approved dose 300 mg bd at the patient's next treatment cycle.

Olaparib tablets should be swallowed whole and not chewed, crushed, dissolved or divided. The tablets can be taken with or without food. If vomiting occurs shortly after the olaparib tablets are swallowed, the dose should only be replaced if all of the intact tablets can be seen and counted. Should any patient enrolled on the study miss a scheduled dose for whatever reason (eg, as a result of forgetting to take the tablets or vomiting), the patient will be allowed to take the scheduled dose up to a maximum of 2 hours after that scheduled dose time. If greater than 2 hours after the scheduled dose time, the missed dose is not to be taken and the patient should take their allotted dose at the next scheduled time.

Ceralasertib

Ceralasertib will be supplied as 20 mg, 80 mg, or 100 mg film coated tablets. Patients will be administered ceralasertib od at 160 mg from Day 1 to Day 7 (inclusive) of every 28-day cycle. A total of 160 mg of ceralasertib tablets should be taken at the same time on each day of dosing with approximately 250 mL of water. When ceralasertib is taken in combination with

olaparib, it is advised that it is taken at the same time of day. Ceralasertib tablets should be swallowed whole and not chewed, crushed, dissolved or divided. Patients must fast (water to drink only) from at least 2 hours prior to taking their ceralasertib dose to at least 1 hour post-dose for all doses. No fasting restrictions apply when olaparib is taken on its own.

If vomiting occurs shortly after the ceralasertib tablets are swallowed, the patient should be instructed not to retake the dose, but wait until the next scheduled dose of ceralasertib. If no dose is scheduled for the following day, the dose will not be made up. If a patient misses a scheduled dose (e.g. as a result of forgetting to take the tablets), the patient will be allowed to take the scheduled dose up to a maximum of 2 hours after that scheduled dose time. If greater than 2 hours after the scheduled dose time, the missed dose is not to be taken and the patient should take their allotted dose at the next scheduled time.

Medication accountability should be completed at Day 1 of each Cycle (Table 4 and Table 5).

AZD1775 - this treatment arm was closed following the ISRC meeting on the 17 April 2019

AZD1775 will be supplied as capsules containing 25 mg, 50 mg, 75 mg, 100 mg, or 200 mg of drug substance. AZD1775 will be provided by AstraZeneca. Patients will be administered AZD1775 bd at 150mg from Day 1 to Day 3 (inclusive) and Day 8 to Day 10 (inclusive) of every 21 day cycle. AZD1775 capsules should be swallowed whole and not chewed, crushed, dissolved or divided. AZD1775 should be taken with approximately 250 mL of water approximately 2 hours before or 2 hours after food. These restrictions should be applied to the AZD1775+olaparib treatment arm.

If a patient misses one of the two daily doses according to schedule, the dose should be taken as soon as possible, but not more than 6 hours after the missed dose was scheduled. If greater than 6 hours, the missed dose should be skipped and the patient should take the next dose when scheduled.

If vomiting occurs after a patient takes the AZD1775 dose, the patient should be instructed not to retake the dose, but to wait until the next scheduled dose of AZD1775. If no dose is scheduled for the following day, the dose will not be made up. If vomiting persists, the patient should contact the Investigator.

AZD1775 dosing compliance will be reviewed with the patient at the beginning of each new treatment cycle when study drug is dispensed. All patients will be required to complete a dosing diary, which must be returned to the clinic for review at each visit. The patient should be instructed to record each date and time the dose(s) were taken in the dosing diary. If a dose is missed, the reason must be noted in the diary. A copy of the dosing diary is provided in the study reference materials.

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

All Treatment Arms

Patients will continue with the study treatment until objective disease progression (determined by RECIST 1.1) as long as in the Investigator's opinion they are benefiting from treatment and they do not meet any other discontinuation criteria.

Once patients have been discontinued from study treatment, other treatment options will be at the discretion of the Investigator.

Dose Reductions

For guidance on dose reductions for management of AEs refer to section 6.8. For guidance on dose reductions when concomitant strong or moderate CYP3A inhibitors cannot be avoided see section 7.7.

7.3 Labelling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. Label text will be translated into local language.

7.4 Storage

All study drugs should be kept in a secure place under appropriate storage conditions (at room temperature). The IP label on the bottle specifies the appropriate storage.

7.5 Compliance

The administration of all study drugs (including IPs) should be recorded in the appropriate sections of the eCRF.

Patients should be given clear instructions on how and when to take their study treatment. Patients will self-administer study treatment. Study site staff will make tablet counts at regular intervals during treatment. Compliance will be assessed by the tablet count and the information will be recorded in the appropriate section of the eCRF. After the tablet count has been performed, the remaining tablets will not be returned to the patient but will be retained by the investigative site until reconciliation is completed by the study monitor. All patients must return their bottle(s) of study treatment at the appropriate scheduled visit, when a new bottle will be dispensed. Patients will be instructed to notify study site personnel of missed doses. Dates of missed or held doses will be recorded by the site staff on the eCRF.

Patients must return all containers and any remaining tablets at the end of the study.

7.6 Accountability

The study drug provided for this study will be used only as directed in the Clinical Study Protocol.

The study site staff will account for all study drugs dispensed to and returned from the patient.

At the end of the study, it must be possible to reconcile delivery records with records of usage and destroyed/returned stock. Records of usage should include the ID of the person to whom the study treatment was dispensed, the quantity and date of dispensing and unused study treatment returned to the Investigator. This record is in addition to any drug accountability information recorded on the eCRF. Any discrepancies must be accounted for on the appropriate forms. Certificates of delivery and return must be signed, preferably by the Investigator or a pharmacist, and copies retained in the Investigator site file. Dispensing and accountability records will continue to be collected for as long as patients continue to receive study treatment, although they will not be entered on the database after the database has closed. Study site personnel, if applicable, or the AstraZeneca monitor will account for all study drugs received at the site, unused study drugs and for appropriate destruction. Certificates of delivery, and destruction should be signed.

7.7 Concomitant and other treatments

The use of any natural/herbal products or other traditional remedies should be discouraged, but use of these products, as well as use of all vitamins, nutritional supplements, and all other concomitant medications must be recorded in the eCRF.

Medications that may NOT be administered (All Treatment Arms)

No other anti-cancer therapy (chemotherapy, immunotherapy, hormonal therapy (hormone replacement therapy is acceptable), radiotherapy, biological therapy or other novel agent) is to be permitted while the patient is receiving study medication.

Live virus and live bacterial vaccines should not be administered whilst the patient is receiving study medication and during the 30-day follow up period. An increased risk of infection by the administration of live virus and bacterial vaccines has been observed with conventional chemotherapy drugs and the effects with olaparib are unknown.

Restricted concomitant medications

Olaparib:

Strong or Moderate CYP3A inhibitors

Known strong CYP3A inhibitors (eg, itraconazole, telithromycin, clarithromycin, boosted protease inhibitors, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil) should not be taken with study treatment.

If there is no suitable alternative concomitant medication then the dose of study treatment should be reduced for the period of concomitant administration. The dose reduction of study treatment should be recorded in the eCRF with the reason documented as concomitant CYP3A inhibitor use.

- Strong CYP3A inhibitors – reduce the dose of olaparib to 100 mg bd for the duration of concomitant therapy with the strong inhibitor and for 5 half-lives afterwards.

- Moderate CYP3A inhibitors - reduce the dose of olaparib to 150 mg bd for the duration of concomitant therapy with the moderate inhibitor and for 3 half-lives afterwards.

- After the washout of the inhibitor is complete, the study treatment dose can be re-escalated.

Strong or moderate CYP3A inducers

Strong (eg, phenobarbital, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine, enzalutamide and St John's Wort) and moderate CYP3A inducers (eg. bosentan, efavirenz, modafinil) of CYP3A should not be taken with study treatment.

If the use of any strong or moderate CYP3A inducers are considered necessary for the patient's safety and welfare this could diminish the clinical efficacy of olaparib.

If a patient requires use of a strong or moderate CYP3A inducer then they must be monitored carefully for any change in efficacy of study treatment.

Permeability glycoprotein (P-gp) inhibitors

It is possible that co-administration of P-gp inhibitors (eg amiodarone, azithromycin) may increase exposure to olaparib. Caution should therefore be observed.

Effect of olaparib on other drugs

Based on limited *in vitro* data, olaparib may increase the exposure to substrates of CYP3A4, P-gp, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K.

Based on limited *in vitro* data, olaparib may reduce the exposure to substrates of CYP3A4, 2B6, 2C9, 2C19 and P-gp.

The efficacy of hormonal contraceptives may be reduced if co administered with olaparib.

Caution should therefore be observed if substrates of these isoenzymes or transporter proteins are co-administered.

Examples of substrates include:

- CYP3A4 – hormonal contraceptive, simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and quetiapine.

- CYP2B6 – bupropion, efavirenz.

- CYP2C9 – warfarin.

- CYP2C19 - lansoprazole, omeprazole, S-mephenytoin.

- P-gp - simvastatin, pravastatin, digoxin, dabigatran, colchicine.
- OATP1B1 - bosentan, glibenclamide, repaglinide, statins and valsartan.
- OCT2 - serum creatinine.

Ceralasertib

Ceralasertib is an investigational drug for which potential interaction is considered on the basis of preclinical *in vitro* data only. As ceralasertib is being administered in combination with Olaparib, potential interactions of the Olaparib should also be considered.

The principal enzyme for metabolising ceralasertib is CYP3A, with some contribution by CYP2C8.

- If the use of any strong inhibitors of CYP3A and/or CYP2C8 is considered necessary for the patient's safety and welfare, the investigator must interrupt ceralasertib for the duration of concomitant therapy with the CYP3A and/or CYP2C8 inhibitor and required washout period (5 half-lives for strong and moderate CYP3A inhibitors). If the use of any strong inducers of CYP3A and/or CYP2C8 is considered necessary for the patient's safety and welfare, this may diminish the clinical efficacy of ceralasertib and the patient should be monitored for any change in the efficacy of study treatment.
- Ceralasertib is a Pgp substrate. Co-administration of Pgp inhibitors or inducers may affect exposure to ceralasertib and, therefore, should not be coadministered with ceralasertib. If the use of any inhibitors or inducers of Pgp are considered necessary for the subject's safety and welfare, the investigator must interrupt ceralasertib for the duration of the Pgp inhibitor or inducer and wait for the required wash-out period of the Pgp modulator (five half-lives) before dosing ceralasertib again.
- Ceralasertib is also a substrate of BCRP. Co-administration of BCRP inhibitors or inducers may affect exposure to ceralasertib; therefore, it is recommended that the investigators must interrupt ceralasertib for the duration of the BCRP inhibitor or inducer and wait for the required wash-out period of the BRCP modulator (five half-lives) before dosing ceralasertib again.
- Ceralasertib is a potential inducer of CYP3A4 and CYP2B6. Caution should be applied with coadministration of drugs that are either completely metabolized by CYP3A4 and/or CYP2B6, or that are substrates of CYP3A4 and/or CYP2B6 and also have a narrow therapeutic index. Investigators should be aware that the exposure of other drugs metabolised by CYP3A4 and/or CYP2B6 may be reduced.
- Ceralasertib is an inhibitor of OATP1B1 and BCRP. Caution should be applied with coadministration of substrates of OATP1B1 and/or BCRP as ceralasertib may increase their exposure.

If the use of any strong inducers or inhibitors of CYP3A4 and/or CYP2C8 is considered necessary for the patient's safety and welfare, the Investigator must contact the trials office and a decision to allow the patient to continue in the study will be made on a case-by-case basis.

A non-exhaustive list of restrictive and/or prohibited drugs is provided in Appendix I

AZD1775 - Not applicable following CSPv6.0

For concomitant and other treatments in combination with AZD1775 see Appendix H.

All Treatment Arms:

Anticoagulant therapy

Patients who are taking warfarin may participate in this study; however, it is recommended that INR be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Subcutaneous heparin, low molecular weight heparin and non-vitamin K antagonist oral coagulants (NOACs) are permitted.

Haematological support

Haematological toxicity should be appropriately managed as outlined in section 6.8.1. Blood / platelet transfusions may be given at the discretion of the Investigator according to local hospital guidelines, and recorded in the eCRF. The use of erythropoietin is not permitted. Intravenous iron is permitted if required by a patient on study, but not prior to dosing.

Primary prophylaxis with G-CSF is not permitted. However, if a patient develops febrile neutropenia, study treatments should be stopped and appropriate management including G-CSF should be given according to local hospital guidelines (see Section 6.8.1.2).

Anti-emetics/anti-diarrhoeals

From screening part 2 onwards, should a patient develop nausea, vomiting and / or diarrhoea, then these symptoms should be reported as AEs (see Section 6.3) and appropriate treatment of the event given. Antiemetic prophylaxis as mandated by the protocol should be recorded as concomitant medication. Please note: aprepitant (Emend) and fosaprepitant are not permitted in the olaparib+AZD1775 treatment arm due to known DDIs - N**o longer applicable following CSPV6.0, provided there has been a minimum washout period of 10 days since the final dose of AZD1775.**

Palliative radiotherapy

Palliative radiotherapy may be used for the treatment of pain at the site of bony metastases that were present at baseline, provided the Investigator does not feel that these are indicative of clinical disease progression during the study period. Study treatment should be discontinued for a minimum of 3 days before a patient undergoes therapeutic palliative

radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.

Administration of other anti-cancer agents

Patients must not receive any other concurrent anti-cancer therapy, including investigational agents, while on study treatment. Patients may continue the use of bisphosphonates or denosumab for bone disease as long as these were started at least 5 days prior to study treatment. If on corticosteroids for the symptomatic control of brain metastases, the patient should be receiving a stable dose of corticosteroids started at least 4 weeks prior to treatment.

Subsequent therapies for cancer

Details of first and subsequent therapies for cancer and/or details of surgery for the treatment of the cancer, after discontinuation of treatment, will be collected. Reasons for starting subsequent anti-cancer therapies including access to other PARP inhibitors or investigational drugs will be collected and included in the assessments of OS.

7.7.1 Other concomitant treatment

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

Following the final PFS analysis data cut off for a stratum (either non HRR*m*, *BRCAm* and/or non *BRCAm* HRR*m*) concomitant medications should be recorded in the patient notes **but not** recorded in the eCRF

In addition, any unplanned diagnostic, therapeutic or surgical procedure performed during the study period must be recorded in the eCRF.

Following the final PFS analysis data cut off for a stratum (either non HRR*m*, *BRCAm* and/or non *BRCAm* HRR*m*) unplanned diagnostic, therapeutic or surgical procedures should be recorded in the patient notes **but not** recorded in the eCRF.

8. STATISTICAL ANALYSES BY ASTRAZENECA

8.1 Statistical considerations

Statistical analyses will be performed by AstraZeneca or its representatives including CROs. Further details of the statistical analysis will be described in an SAP.

Patient populations related to the study objectives

Statistical analyses will be done for up to 5 patient populations based on the tumour biomarker strata A, B, C.

- "*BRCAm*" = patients from stratum A
- "HRR*m*" = patients from stratum A and patients from stratum B
- "Non *BRCAm*HRR*m*" = patients from stratum B
- "All" = patients from any stratum
- "Non HRR*m*" = patients from stratum C

Primary statistical analyses comparing PFS based on BICR for each combination treatment arms to olaparib will be conducted for the 3 patient populations *BRCAm*, Non *BRCAm* HRR*m* and Non HRR*m*.

Comparisons of PFS based on BICR for each of the combination treatment arms to olaparib in the 2 patient populations HRR*m* and All will be conducted as secondary statistical analyses.

Secondary outcome measures will be analysed for the 3 patient populations *BRCAm*, Non *BRCAm* HRR*m* and Non HRR*m*, except

- OR and OS, which will be analysed for all 5 patient populations
- Tumour and germline mutation status, which will be analysed only for the All patient population
- PK outcome measures, which will be analysed only for the All patient population

RECIST-based primary and secondary outcome measures based on Investigator assessments will also be analysed for sensitivity purposes.

Safety outcome measures and exploratory outcome measures will be analysed for the All patient population, except CCI which will be analysed for all 5 patient populations.

Handling of multiplicity

Multiplicity adjustment will be considered within each of the 3 primary patient populations for PFS. The overall alpha for each primary patient population will be 0.2, and a simple Bonferroni adjustment assigns alpha of 0.1 to each of the 2 pairwise treatment arm comparisons to olaparib.

No further adjustments for multiplicity are planned.

Overview of timings of interim and final analyses

For the non HRR*m* population an interim futility analysis will be triggered when 75 patients have been recruited and assessed for at least 8 weeks, in order to assess the proportion of patients with Non Progressive Disease (NPD), based on the Investigator assessment at

8 weeks in each of the treatment arms. Recruitment will be paused after the 75th patient has been recruited into this population, until the AZ URC confirms which treatment arms should be reopened.

A further NPD futility interim analysis in the non *BRCAm* HRR*m* population may be performed, if the outcome of the interim analysis in the non HRR*m* population resulted in treatment arms being stopped.

For each of the 3 primary patient populations (non HRR*m*, *BRCAm* and non *BRCAm* HRR*m*) a further interim analysis for PFS is triggered when 44 PFS events for the ceralasertib +olaparib vs. olaparib monotherapy pairwise comparison in that particular patient population have occurred. As the non HRR*m* patient population is expected to be enrolled quicker than the other patient populations, it is expected the interim analysis for this patient population will occur first, followed by interim analysis for the 2 other primary patient populations. These PFS interim analyses may be concurrent or separate depending on the recruitment and PFS event rates for the 3 patient populations and other operational requirements.

For each of the 3 primary patient populations (non HRR*m*, *BRCAm* and non *BRCAm* HRR*m*) the final analysis for PFS is triggered when 68 PFS events for the ceralasertib + olaparib vs. olaparib monotherapy pairwise comparison in that particular patient population have occurred. These final analyses may be concurrent or separate depending on the recruitment and PFS event rates for the 3 patient populations and other operational requirements.

An initial OS analysis will be performed at the same time as the primary analysis of PFS. A further analysis of OS will be performed when the OS data for the ceralasertib + olaparib vs. olaparib monotherapy pairwise comparison is approximately 70% mature.

8.2 Sample size estimate

In the 3 tumour biomarker strata A, B, C, for each of the 2 comparisons (ceralasertib + olaparib vs olaparib monotherapy, AZD1775 + olaparib vs olaparib monotherapy), 68 PFS events would have 80% power to show a statistically significant difference at the two-sided 10% significance level if the assumed true treatment effects were HR 0.55. This translates to a 5-month benefit in median PFS over 6 months on olaparib in the *BRCAm* stratum and a 4.17-month benefit in median PFS over 5 months on olaparib in the non *BRCAm* HRR*m* stratum and in the non HRR*m* stratum if PFS is exponentially distributed.

Following the decision of the ISRC to close recruitment to the AZD1775 + olaparib arm, the study will only be sized to detect a difference for the ceralasertib + olaparib vs olaparib monotherapy comparison.

Approximately 50 patients (450 patients overall) will be randomised to each of the 3 treatment arms within each of the 3 biomarker strata so that data maturity for the PFS analysis is approximately 68%. Following the closure of the olaparib+AZD1775 arm in April 2019, fewer than 50 patient per strata will be randomised to this arm and the total number of patients randomised will be lower (approximately 350 patients).

Assuming 15 months non linear recruitment, the required number of PFS events are expected to occur approximately 24 months after the first patient is randomised.

8.3 Definitions of analysis sets

8.3.1 Full analysis set

The full analysis set (FAS) will include all randomised patients with treatment groups assigned in accordance with the randomisation, regardless of the treatment actually received. Patients who were randomised but did not subsequently receive treatment are included in the FAS. The analysis of data using the FAS therefore follows the principles of intent to treat (ITT). All efficacy and CCI data will be summarised and analysed using the FAS. Disposition, demographic data, baseline characteristics, etc will be summarized using the FAS.

8.3.2 Safety analysis set

The safety analysis set will include all patients who received at least one dose of randomised treatment (regardless of whether that was the randomised therapy intended or indeed whether, in rare cases, they received therapy without being randomised), according to the treatment they actually received (the detailed definition of "treatment received" will be included in the SAP). All safety data will be summarised and analysed using the safety analysis set. Drug exposure will be summarized using the safety analysis set.

8.3.3 PK analysis set

All patients who received at least one dose of study treatment per the protocol and for whom there is at least one reportable PK concentration will be included in the PK analysis set.

8.4 Outcome measures for analyses

8.4.1 Primary outcome measure (Calculation or derivation of efficacy variables)

Blinded Independent Central Review of RECIST based assessments

The BICR of radiological imaging data will be carried out using RECIST version 1.1. All radiological scans for all patients (including those at unscheduled visits, or outside visit windows) will be provided to the BICR. The imaging scans will be reviewed by two independent radiologists using RECIST 1.1 criteria and will be adjudicated if required. The independent reviewers will be blinded to study treatment. BICR data will be used to determine the endpoints PFS, objective response, DoR, and tumour change for primary and secondary analyses.

For each visit, patients will be programmatically assigned a RECIST 1.1 visit response of CR, PR, SD or PD depending on the status of their disease compared with baseline and previous assessments. If a patient has had a tumour assessment, which cannot be evaluated, then the patient 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.

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

Investigator RECIST based assessments

From the Investigators review of the imaging scans, the RECIST tumour response data will be used to determine each patient's visit response according to RECIST version 1.1. It will be used to determine the endpoints PFS, objective response, DoR, and tumour change for sensitivity analyses.

At each visit, patients will be programmatically assigned a RECIST 1.1 visit response of CR, PR, SD or PD depending on the status of their disease compared with baseline and previous assessments. If a patient has had a tumour assessment, which cannot be evaluated, then the patient will be assigned a visit response of NE (unless there is evidence of progression in which case the response will be assigned as PD).

Please refer to Appendix F for the definitions of CR, PR, SD and PD.

PFS

Progression free survival is defined as the time from randomisation until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from randomised therapy or receives another anti-cancer therapy prior to progression. Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST assessment.

However, if the patient progresses or dies after two or more missed visits, the patient will be censored at the time of the latest evaluable RECIST assessment. If the patient has no evaluable visits or does not have baseline data they will be censored at 0 days unless they die within two visits of baseline: in such a case, the death date will be used as the event date.

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

RECIST assessments/scans contributing towards a particular visit may be performed on different dates. The following rules will be applied:

Date of progression will be determined based on the earliest of the dates of the component that triggered the progression.

When censoring a patient for PFS, the patient will be censored at the latest of the dates contributing to a particular overall visit assessment.

ORR

The ORR will be defined using the BICR data to define a visit response of CR or PR, with the denominator defined as subset of all randomised patients with measurable disease at baseline per BICR. For sensitivity analysis, ORR is defined as the percentage of patients with at least

one Investigator-assessed visit response of CR or PR and will be based on a subset of all randomised patients with measurable disease at baseline per the site Investigator.

Data obtained up until progression, or last evaluable assessment in the absence of progression, will be included in the assessment of ORR. Patients who discontinue randomised treatment without progression, receive a subsequent anti-cancer therapy (note that for this analysis radiotherapy is not considered a subsequent anti-cancer therapy) and then respond will not be included as responders in the ORR.

DoR

The DoR will be defined as the time from the date of first documented response according to BICR data until date of documented progression according to BICR data or death in the absence of disease progression (ie, date of PFS event or censoring – date of first response + 1). The end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. The time of the initial response will be defined as the latest of the dates contributing towards the first visit response of PR or CR.

For sensitivity analysis, DoR is defined as the time from the date of first documented response according to Investigator assessment until date of documented progression according to Investigator assessment or death in the absence of disease progression (ie, date of PFS event or censoring – date of first response + 1).

If a patient does not progress following a response, then their DoR will use the respective PFS censoring time.

Tumour size change

Absolute change and percentage change from baseline in TLs tumour size at 16 weeks will be based on RECIST TLs measurements taken at baseline and at Week 16. Tumour size is the sum of the longest diameters of the TLs. Baseline for RECIST is defined to be the last evaluable assessment prior to randomisation.

The percentage change in TL tumour size at Week 16 will be obtained for each patient taking the difference between the sum of the TLs at Week 16 and the sum of the TLs at baseline divided by the sum of the TLs at baseline times 100 (ie (Week 16 - baseline)/baseline * 100).

The absolute change in TL tumour size at Week 16 will be obtained for each patient by the difference between the sum of the TL at Week 16 and the sum of the TLs at baseline.

Handling of missing data will be described in the SAP.

OS

Overall survival is defined as the time from the date of randomisation until death due to any cause. Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive.

Note: Survival calls will be made in the 2 weeks following the date of the data cut-off for each OS analysis, and if patients are confirmed to be alive, or if the death date is post the final data cut-off date, these patients will be censored at the date of the final data cut off. Death dates may be found by checking publicly available death registries.

CCI

CCI will be described in the SAP.

Non Progressive Disease (Futility Interim only)

NPD will be assessed 8 weeks after dosing and is defined as the proportion of all patients dosed that have a visit response of SD, PR or CR at Week 8. Earlier visit responses of CR, PR that become PD at Week 8 or NE responses at Week 8 do not constitute NPD at 8 weeks.

A time window around the Week 8 visit will be applied, such that any visits occurring 7 weeks or more after dosing are acceptable; however, if an earlier visit is defined as PD then the visit response at Week 8 would also be defined as PD. If the Week 8 response is missing or NE but the next evaluable response is SD or better then the patient will be defined as having NPD at 8 weeks.

8.4.2 Secondary outcome measures (Calculation or derivation of safety variables)

Safety and tolerability will be assessed in terms of AEs, deaths, laboratory data, vital signs, ECG data and ECOG PS. These will be collected for all patients.

Adverse events

AEs (both in terms of Medical Dictionary for Regulatory Activities [MedDRA] preferred terms and CTCAE grade) will be listed individually by patient.

Any AE occurring within 28 days of discontinuation of IP will be included in the AE summaries. Any events in this period that occur after a patient has received further therapy for cancer (following discontinuation of IP) will be flagged in the data listings.

Other significant AEs (OAEs)

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

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

8.4.3 Safety outcome measures (Calculation or derivation of pharmacokinetic variables)

Given the sparse PK schedule, the PK parameters will be derived using population PK modelling. The results of any such analyses will be reported separately from the CSR.

8.5 Methods for statistical analyses

All efficacy analyses will be performed on the FAS. Results of statistical analyses will be presented using 90% CIs and 2-sided p-values.

Pairwise comparisons between the ceralasertib + olaparib vs. olaparib monotherapy, AZD1775+olaparib vs. olaparib monotherapy and ceralasertib + olaparib vs. AZD1775+olaparib will be generated for each endpoint.

Following the decision of the ISRC to close recruitment to the AZD1775 + olaparib arm, the study will only be sized to detect a difference for the ceralasertib + olaparib vs olaparib monotherapy comparison, although all the available data across all 3 arms, where possible, will be used in the statistical models.

As the starting dose of the AZD1775+Olparib arm was refined during the study, for any comparisons including the AZD1775+olaparib arm, all AZD1775+olaparib patients regardless of their starting dose will be included in the analyses. Additional sensitivity analyses may be carried out which only including those patients AZD1775+Olaparib patients who start treatment on the revised starting dose.

The assignment of a patient to each of the populations will be based on the values entered into IVRS at randomisation, even if it is subsequently discovered that these values were incorrect or not confirmed by the central FMI assay. If there are any patients who were wrongly assigned, a sensitivity analysis may be carried out with patients in the population they should have been assigned to.

The stratification in the statistical modelling will be based on the values entered into IVRS at randomisation, even if it is subsequently discovered that these values were incorrect. If there are any patients who were mis-stratified, a sensitivity analysis will be carried out using the (correct) baseline data collected in the eCRF.

8.5.1 Analysis of the primary variable (s)

Primary analysis of PFS will be based on data from the BICR; sensitivity analyses of PFS are described further below.

Patient populations: *BRCAm*, *non BRCAm HRRm*, non HRR*m* (primary analysis)

In each of these patient populations, PFS will be analysed using pair-wise log rank tests (using the Breslow approach for handling ties) stratified by prior platinum-based therapy for generation of the p-value.

The pairwise HRs and confidence intervals will be estimated from a stratified Cox Proportional Hazards model (with ties = Efron) with a prior platinum-based therapy (Y/N) term included in the strata statement and the CIs calculated using a profile likelihood approach.

For each patient population, a KM plot of PFS will be presented by treatment group (overall and stratified by prior platinum-based therapy).

Patient population: HRR*m* (secondary analysis)

To achieve an estimated pairwise HRs for PFS that are representative of the HRR*m* patient population, the following approach will be implemented:

1. PFS will be analysed using pair-wise log rank tests (using the Breslow approach for handling ties) stratified by prior platinum-based therapy separately in stratum A and stratum B

2. pair-wise HRs (separately for stratum A and stratum B) will be obtained directly from the Cox Proportional Hazard Model

3. a weighted estimate of the $HR_{\mathrm{HRR}m}$ will be calculated using the estimated HR in stratum A (HR_A) and the estimated HR in stratum B (HR_B):

   $$ln(HR_{\mathrm{HRR}m}) = w_1 ln(HR_A) + w_2 ln(HR_B)$$

   where weights w_1 and w_2 will be estimated from external literature and the study's screening records

4. For calculation of CIs, the overall variance (log scale) will take into account the variance of both groups (that are independent), and thus be calculated as:

   $$var(ln(HR_{\mathrm{HRRm}})) = w_1^2\, var(ln(HR_A)) + w_2^2\, var(ln(HR_B))$$

As a sensitivity analysis, PFS will be analysed using an unweighted log rank test stratified by biomarker status (stratum A, stratum B) and prior platinum-based therapy for generation of the p-value and using the Breslow approach for handling ties.

The pairwise HRs and confidence intervals will be estimated from a stratified Cox Proportional Hazards model (with ties = Efron) with biomarker status (stratum A, stratum B) and a prior platinum-based therapy (Y/N) term included in the strata statement and the CIs calculated using a profile likelihood approach.

KM plots of PFS will be presented by treatment group (overall and stratified by prior platinum-based therapy).

Patient population: All (secondary analysis)

Similar weighted and unweighted analyses as described above will be conducted for the All patient population; now with 3 weights to combine the HR estimates and its variances for the 3 strata A, B and C.

Sensitivity analyses for the 3 primary analyses of PFS

(a) Ascertainment bias

The possibility of bias in assessment and measurement of PFS by BICR will be assessed by comparing the HRs derived from BICR with the HR derived using the Investigators' review assessment of disease progression by RECIST.

(b) Evaluation-time bias

In order to assess possible evaluation-time bias, that could occur if scans are not performed at the protocol-scheduled time points, the midpoint between the time of progression and the previous evaluable RECIST assessment will be analysed using a stratified log rank test, as described for the primary analysis of PFS. For patients who die in the absence of progression, the date of death will be used to derive the PFS time used in the analysis.

(c) Attrition bias

Possible attrition bias will be assessed by repeating the primary PFS analysis, except that the actual PFS event times, rather than the censored times, of patients who progressed or died in the absence of progression immediately following two, or more, non evaluable tumour assessments will be included. In addition, patients who take subsequent therapy prior to progression or death will be censored at their last evaluable assessment prior to taking the subsequent therapy. A KM plot of the time to censoring, where the censoring indicator of the primary PFS analysis is reversed, will be presented.

8.5.2 Secondary analyses

Secondary analyses will be performed for the patient populations defined earlier, and according to the overview below.

Patient Population	Secondary Objectives	Outcome Measures
• HRR*m* • All	To assess the efficacy of the combination of ceralasertib +olaparib and the combination of AZD1775+olaparib compared with olaparib monotherapy by assessment of PFS	PFS using Blinded Independent Central Review (BICR) according to Response Evaluation Criteria in Solid Tumours (RECIST 1.1) Sensitivity analysis of PFS using Investigator assessments according to RECIST 1.1

Patient Population	Secondary Objectives	Outcome Measures
• *BRCAm* • HRR*m* • Non *BRCAm* HRR*m* • All • Non HRR*m*	To assess the efficacy of the combination of ceralasertib +olaparib and the combination of AZD1775+olaparib compared with olaparib monotherapy in terms of • ORR	Objective response using BICR according to RECIST 1.1 Sensitivity analysis of objective response using Investigator assessments according to RECIST 1.1
• *BRCAm* • Non *BRCAm* HRR*m* • Non HRR*m*	To assess the efficacy of the combination of ceralasertib +olaparib and the combination of AZD1775+olaparib compared with olaparib monotherapy in terms of • DoR • tumour change	DoR and tumour change using BICR according to RECIST 1.1 Sensitivity analysis of DoR, and tumour change using Investigator assessments according to RECIST 1.1
• *BRCAm* • HRR*m* • Non *BRCAm* HRR*m* • All • Non HRR*m*	To assess the efficacy of the combination of ceralasertib +olaparib and the combination of AZD1775+olaparib compared with olaparib monotherapy in terms of OS	Time to death for any cause
• *BRCAm* • HRR*m* • Non *BRCAm* HRR*m* • All • Non HRR*m*	To compare the efficacy of the combination of ceralasertib +olaparib with the combination of AZD1775+olaparib in terms of • PFS • ORR	PFS and objective response using BICR according to RECIST 1.1 Sensitivity analysis of PFS and objective response using Investigator assessments according to RECIST 1.1
• *BRCAm* • Non *BRCAm* HRR*m* • Non HRR*m*	To compare the efficacy of the combination of ceralasertib +olaparib with the combination of AZD1775+olaparib in terms of • DoR • tumour change	DoR and tumour change using BICR according to RECIST 1.1 Sensitivity analysis of DoR and tumour change using Investigator assessments according to RECIST 1.1
• *BRCAm* • HRR*m* • Non *BRCAm* HRR*m* • All • Non HRR*m*	To compare the efficacy of the combination of ceralasertib +olaparib with the combination of AZD1775+olaparib in terms of OS	Time to death for any cause

Patient Population	Secondary Objectives	Outcome Measures
• All	To explore the frequency of and describe the nature of tumour HRR (including *BRCA*) mutation(s) in tumour samples and to compare this with germline HRR (including *BRCA*) mutation status	Tumour and germline mutation status of CCI genes
• All	To assess exposure to olaparib, ceralasertib and AZD1775 in all patients	$C_{min\ ss}$

For patient populations based on single tumour gene-based strata, unweighted analyses will be conducted; for patient populations based on a combination of tumour gene-based strata, weighted analyses (with weights derived as described in Section 8.5.1) will be conducted.

8.5.2.1 Analysis of objective response

Objective response will be analysed using logistic regressions with a covariates study treatment and prior platinum-based therapy. The results of the analysis will be presented in terms of an odds ratio for study treatments together with associated 90% profile likelihood CI and 2-sided p-values. P-values will be based on twice the change in log-likelihood resulting from the addition of covariate study treatment to the model containing only the covariate related to prior platinum-based therapy.

8.5.2.2 Analysis of DoR

In order to analyse the secondary outcome variable, DoR between treatment arms, the Expected Duration of Response (EDoR) will be derived for each treatment arm. The EDoR is the product of the proportion of patients responding to treatment and the mean DoR in responding patients, and provides an estimate based on all randomised patients.

Study treatments will be compared (stratified for prior platinum-based therapy) by calculating pair-wise ratios of EDoRs (including 90% CIs) using an appropriate probability distribution for DoR in responding patients. The choice of probability distribution will be detailed in the SAP.

Additionally, descriptive data will be provided for the DoR in responding patients, including associated KM curves.

8.5.2.3 Analysis of Tumour Size Change at Week 16

The absolute change in TL tumour size from baseline and percentage change in TL tumour size from baseline will be summarized using descriptive statistics by study treatment.

The effect of study treatments on absolute and percentage change in TLs tumour size at Week 16 will be estimated from an analysis of covariance model including a term for the absolute (percentage) change in Week 16 value, a covariate for baseline TLs tumour size, a covariate for prior platinum-based therapy and a covariate for the time from the baseline scan to randomisation. The number of patients, unadjusted mean and least-squares means for each treatment arm will be presented, together with the difference in least-squares means, 90% Cis and corresponding 2-sided p-values.

8.5.2.4 Analysis of OS

OS data will be analysed using the same methodology and model as for the analysis of PFS described in Section 8.5.1 (provided there are sufficient events available for a meaningful analysis, if not, only descriptive summaries will be provided).

8.5.2.5 CCI

The statistical analysis of the CCI variables will be described in the SAP.

8.5.2.6 Pharmacokinetics

Plasma concentrations for each of the drug substances measured within each of the treatment arms together with any associated metabolites will be listed by nominal sample time. In addition, minimum concentrations at steady state ($C_{min\ ss}$) will be summarised using appropriate summary statistics. Further details will be provided in the SAP.

The plasma concentration data for olaparib, AZD1775 and/or ceralasertib will be analysed using a population PK approach, which may include exploring the influence of covariates on PK where appropriate and may be combined with other studies' data. In addition, a population PDx approach will be used to investigate the relationship between PK and selected primary, secondary, and/or exploratory endpoints, where deemed appropriate.

The data analysis plan and results of such population PK and PKPDx analyses will be reported separately from the CSR.

8.5.3 Safety and tolerability variables

- Safety and tolerability variables will be summarized descriptively by treatment arm for the Safety Analysis Set:

- AEs, laboratory test results, categorical ECG data and ECOG PS will be summarized by incidence estimates, overall and by CTCAE grading (laboratory tests in addition also by shift tables), where applicable.

Time course of laboratory test results, vital signs and continuous ECG data will be summarized graphically.

8.5.4 Subgroup analysis (if applicable)

Any additional subgroup analyses will be described in the SAP.

8.5.5 Interim analyses

For the non HRR*m* population an interim analysis will be triggered when 75 patients have been recruited and assessed for at least 8 weeks, in order to assess the proportion of patients with NPD based on the Investigator assessment at 8 weeks in each of the treatment arms. With approximately 25 patients in each treatment arm, if the 80% two-sided upper CI for the proportion of patients with NPD is less than 56% (O'Shaughnessy et al 2014) and with consideration of this analysis in context with the totality of the clinical data (safety and efficacy) available, the URC may recommend to cease recruitment in this arm and no further patients will be recruited into that treatment arm in the non HRRm population. Recruitment will be paused after the 75th patient has been recruited into the population, until the AZ URC confirms the strata and which treatment arms should be reopened.

A further NPD futility interim analysis, using the same criteria, in the non *BRCAm* HRR*m* population may be performed, if the outcome of the interim analysis in the non HRR*m* population resulted in treatment arms being stopped.

As the "non HRR*m*" patient population is expected to be enrolled quicker than the other patient populations, the first PFS interim analysis for patient population "non HRR*m*" is triggered when 44 PFS events for the ceralasertib +olaparib vs. olaparib monotherapy pairwise comparison (65% of planned number of PFS events) have occurred in stratum C.

The second PFS interim analysis for patient populations "*BRCAm*" and "non BRCA*m* HRR*m*" is triggered when 44 PFS events for the ceralasertib +olaparib vs. olaparib monotherapy pairwise comparison (65% of planned number of PFS events) have occurred in each of the two strata A and B.

The PFS interim analyses may be concurrent or separate depending on the PFS event rates in the three strata and operational requirements, so if the timings for the *BRCAm* and non *BRCAm* HRR*m* populations are not concurrent, separate interims may be needed for each patient population. The purpose of the interim analyses is to provide the opportunity (details will be specified in the URC Charter) for an early trigger to commence a phase III study, if the results are strong enough.

An initial OS analysis will be performed at the same time as the primary analysis of PFS and will use the same methodology and model. A further analysis of OS will be performed when the OS data are approximately 70% mature; this is anticipated to occur approximately 42 months after first patient in.

8.5.6 Exploratory analysis

The statistical analysis of exploratory outcome variables will be described in the SAP.

9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA

9.1 Training of study site staff

Before the first patient is entered into the study, an AstraZeneca representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures, CCI [redacted] s and the Clinical Database utilised as well as on the handling of samples for both the local and the central laboratory.

The PI will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The PI will maintain a record of all individuals involved in the study (medical, nursing and other staff).

9.2 Monitoring of the study

During the study, an AstraZeneca representative will have regular contacts with the study site, including visits to:

- Provide information and support to the Investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the Clinical Study Protocol, that data are being accurately and timely recorded in the CRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed.
- Perform source data verification (a comparison of the data in the CRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (eg, clinic charts).
- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient.

The AstraZeneca representative will be available between visits if the Investigator(s) or other staff at the centre needs information and advice about the study conduct.

9.2.1 Source data

The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the eCRF that are transcribed from source documents must be consistent with the source documents, or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Source data includes all information in original records and certified copies of original records or clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial.

Refer to the CSA for location of source data.

9.2.2 Study agreements

The PI at each/the centre should comply with all the terms, conditions, and obligations of the CSA, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the CSA, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the CSA shall prevail.

Agreements between AstraZeneca and the PI should be in place before any study-related procedures can take place, or patients are enrolled.

9.2.3 Archiving of study documents

The Investigator follows the principles outlined in the CSA.

9.3 Study timetable and end of study

Final analysis for PFS per stratum

The data cut off (DCO) for the final analysis for PFS for each of the 3 strata (non HRR*m*, BRCA*m* and non BRCA*m* HRR*m*) will occur when at least 68 PFS events for the ceralasertib +olaparib vs. olaparib monotherapy pairwise comparison in that particular population has occurred.

The database will close to new data entry for patients at the time of the DCO of the final analysis for PFS analysis in each stratum (non HRR*m*, BRCA*m* and non BRCA*m* HRR*m*) is met with the exceptions described below:

Patients on treatment

Patients who are receiving study treatment at the time of the data cut-off can either choose to discontinue from the study or, when the investigator believes patients are gaining clinic benefit, patients may continue to receive study treatment within the study. It is recommended

that the patients continue the scheduled protocol visits and Investigators monitor the patient's safety laboratory results prior to and periodically during treatment with study treatment in order to manage AEs in accordance with the Dose Modification and Toxicity Management Guidelines (see Section 6.8). Data will no longer be required to be entered into the clinical database for the stratum that has met the trigger for the final analysis for PFS with the exception of the following data which must continue to be recorded in the eCRF (Table 6):

1. IP dispensation and accountability
2. Laboratory Safety Assessments
3. Pregnancy Test (In the event of a pregnancy within the reporting timelines outlined in section 6.6 the PREGREP module in the CRF will be completed to report the pregnancy and the PREGOUT will be used to report the outcome of the pregnancy.
4. AEs and SAEs

The required blood sample for CCI at the time of progression should be collected. Wherever possible the optional tumour biopsy should be collected at the time of progression and processed as per the study laboratory manual.

If a patient subsequently discontinues treatment then the 30 days follow up visit should be completed and laboratory safety assessments, pregnancy test and adverse events should be recorded in the eCRF. The patients should then be followed for survival and anti-cancer therapy collected (see Table 4 and Table 5), data should be recorded in the patient notes and captured in the eCRF and reported for the purposes of this study until the Final OS analysis.

Patients in Survival Follow Up

For patients who have discontinued treatment and are in survival follow up at the time of the data cut off for the final analysis for PFS, survival and subsequent cancer therapy data will continue to be collected in the eCRF and reported for the purposes of the study until the final OS Analysis.

All SAEs that occur in patients still receiving study treatment (or within the 30 days following the last dose of study treatment) post the final DCO and database closure must be reported as detailed in Section 6.3.1.

Final OS Analysis

The end of the study is defined as the point that the final OS analysis is completed for all three strata.

Following the data cut off for the final OS Analysis, the clinical study database will close to new data. Patients are, however, permitted to continue to receive study treatment beyond the closure of the database if, in the opinion of the Investigator, they are continuing to receive benefit from treatment with study treatment. For patients who do continue to receive treatment beyond the time of this data cut-off, Investigators will continue to report all SAEs to

AstraZeneca Patient Safety until 30 days after study treatment is discontinued, in accordance with Section 6.4 (Reporting of SAEs). If an Investigator learns of any SAEs, including death, at any time after a patient has completed the study, and he/she considers there is a reasonable possibility that the event is causally related to the IP, the Investigator should notify AstraZeneca, Patient Safety. Additionally, as stated in Section 6.3 (Recording of AEs), any SAE or non serious AE that is ongoing at the time of this data cut-off, must be followed up to resolution unless the event is considered by the Investigator to be unlikely to resolve, or the patient is lost to follow-up.

A Clinical Study Report will be prepared.

The study started in Q1 2018 and to end by approximately Q4 2020.

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 olaparib.

9.4 Data management

All participant data relating to the study will be recorded on the eCRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing he eCRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

Data management will be performed by PAREXEL, according to the Data Management Plan.

The data collected through third party sources will be obtained and reconciled against study data.

Adverse events and medical/surgical history will be classified according to the terminology of the latest version of MedDRA. Medications will be classified according to the World Health Organisation (WHO) Drug Dictionary. All coding will be performed by PAREXEL.

Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The Data Management Plan will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process.

When all data have been coded, validated, signed and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked.

SAE Reconciliation

SAE reconciliation reports are produced and reconciled with the Patient Safety database and/or the investigational site.

Data associated with human biological samples

Data associated with biological samples will be transferred from laboratories internal or external to AstraZeneca.

Management of external data

The data collected through third party sources will be obtained and reconciled against study data.

Data from external providers (eg, central laboratories) will be validated as appropriate to ensure it is consistent with the clinical data and included in the final database. In the case of biomarker (tumour tissue or blood for exploratory analyses) data, the results of any analyses will not be recorded in the database, but information relating to the processing of the sample, including the original date of biopsy (historical tumour tissue sample and the actual date the sample[s] were collected) will be recorded in the eCRF and database.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

- The study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable International Council on Harmonisation (ICH)/Good Clinical Practice (GCP)
- Applicable regulatory requirements

10.2 Patient data protection

Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation. The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of

disclosure and use of their data must also be explained to the participant in the informed consent.

AstraZeneca will not provide individual genotype results to patients, any insurance company, any employer, their family members, general physician, unless required to do so by law**.**

Precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, an AstraZeneca Physician or an Investigator might know a patient's identity and also have access to his or her genetic data. Also Regulatory authorities may require access to the relevant files, though the patient's medical information and the genetic files would remain physically separate.

10.3 Ethics and regulatory review

An Ethics Committee (EC) should approve the final Clinical Study Protocol, including the final version of the Informed Consent Form, Investigator Brochure and any other written information and/or materials to be provided to the patients. The Investigator will ensure the distribution of these documents to the applicable EC, and to the study site staff.

The opinion of the EC should be given in writing. The Investigator should submit the written approval to AstraZeneca before enrolment of any patient into the study.

The EC should approve all advertising used to recruit patients for the study.

AstraZeneca should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

If required by local regulations, the Clinical Study Protocol should be re-approved by the EC annually.

Before enrolment of any patient into the study, the final Clinical Study Protocol, including the final version of the Informed Consent Form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations. Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities. This responsibility may be delegated to a CRO but the accountability remains with AstraZeneca.

AstraZeneca will provide Regulatory Authorities, ECs and PIs with safety updates/reports according to local requirements.

Each PI is responsible for providing the ECs/Institutional Review Board (IRB) with reports of any serious and unexpected ADRs from any other study conducted with the IP. AstraZeneca will provide this information to the PI so that he/she can meet these reporting requirements.

10.4 Financial Disclosure

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

10.5 Informed consent

The PI(s) at each centre will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study.
- Ensure each patient is notified that their participation is voluntary and that they are free to refuse to participate and may withdraw their consent at any time and any reason during the study. Participants of their legally authorized representative will be required to sign an informed consent that meets the requirement of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study centre.
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.
- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study.
- Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File.
- Ensure a copy of the signed Informed Consent Form is given to the patient.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study

- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the informed consent form that is approved by an EC.

10.6 Changes to the Clinical Study Protocol and Informed Consent Form

Study procedures will not be changed without the mutual agreement of the PI and AstraZeneca.

If there are any substantial changes to the Clinical Study Protocol, then these changes will be documented in a new version of the study protocol.

The new version of the Clinical Study Protocol is to be approved by the relevant EC and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for new versions of Clinical Study Protocols.

AstraZeneca will distribute any new versions of the Clinical Study Protocol to each PI(s). For distribution to EC see Section 10.3.

If a change to a Clinical Study Protocol requires a change to a centre's Informed Consent Form, AstraZeneca and the centre's EC are to approve the revised Informed Consent Form before the revised form is used.

10.7 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an EC may perform audits or inspections at the centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the Clinical Study Protocol, GCP, ICH guidelines, and any applicable regulatory requirements. The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the centre.

10.8 Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. The study may be stopped if, in the judgement of AstraZeneca, trial subjects are placed at undue risk because of clinically significant findings that:

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

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

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

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

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

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

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

10.9 Dissemination of Clinical Study Data

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

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Appendix A Additional Safety Information

Further Guidance on the Definition of a Serious Adverse Event (SAE)

Life threatening

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

Hospitalisation

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

Important medical event or medical intervention

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

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

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalisation

Development of drug dependency or drug abuse

A Guide to Interpreting the Causality Question

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

- Time Course. Exposure to suspect drug. Has the patient actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?

- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

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

- Is this a recognized feature of overdose of the drug?

- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.

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

Appendix B International Airline Transportation Association (IATA) 6.2 Guidance Document

Labelling and shipment of biohazard samples

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

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg, Ebola, Lassa fever virus:

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

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

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

Exempt - all other materials with minimal risk of containing pathogens

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

Appendix C Genetic Research

Rationale and Objectives

AstraZeneca intends to collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. Genetic research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in health care and to the discovery of new diagnostics, treatments or medications.

In addition, collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical studies and, possibly, to genetically guided treatment strategies.

Genetic Research Plan and Procedures

Selection of genetic research population

Study selection record

All patients will be asked to participate in this genetic research. Participation is voluntary and if a patient declines to participate there will be no penalty or loss of benefit. The patient will not be excluded from any aspect of the main study.

Inclusion criteria

For inclusion in this genetic research, patients must fulfil all of the inclusion criteria described in the main body of the Clinical Study Protocol **and**:

- Provide informed consent for the genetic sampling and analyses.

Exclusion criteria

Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:

- Previous allogeneic bone marrow transplant
- Non leukocyte depleted whole blood transfusion in 120 days of genetic sample collection

Discontinuation of patients from this genetic research

Specific reasons for discontinuing a patient from this genetic research are:

Withdrawal of consent for genetic research: Patients may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary discontinuation will not prejudice further treatment. Procedures for discontinuation are outlined in Section 7.5 of the main Clinical Study Protocol.

Collection of samples for genetic research

The blood sample for genetic research will be obtained from the patients at Visit 1 or after randomisation. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an adverse event (AE), such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn at Visit 1, it may be taken at any visit until the last study visit. Only one sample should be collected per patient for genetics during the study. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

Coding and storage of DNA samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. Samples will be stored for a maximum of 15 years, from the date of LSLV, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

An additional second code will be assigned to the blood or other appropriate sample type either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable by the second, unique number only. This number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated organization. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organizations working with the DNA).

The link between the patient enrolment/randomisation code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organizations. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent.

Ethical and Regulatory Requirements

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Section 10 of the Clinical Study Protocol.

Informed consent

The genetic component of this study (except for the HRR testing) is optional and the patient may participate in other components of the main study without participating in the genetic component. To participate in the genetic component of the study the patient must sign and date both the consent form for the main study and the genetic component of the study. Copies of both signed and dated consent forms must be given to the patient and the original filed at the study centre. The PI(s) is responsible for ensuring that consent is given freely and that the patient understands that they may freely discontinue from the genetic aspect of the study at any time.

Patient data protection

AstraZeneca will not provide individual genotype results to patients, any insurance company, any employer, their family members, general physician unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, an AstraZeneca Physician or an Investigator might know a patient's identity and also have access to his or her genetic data. Also Regulatory authorities may require access to the relevant files, though the patient's medical information and the genetic files would remain physically separate.

Data management

Any genotype data generated in this study will be stored at a secure system at AstraZeneca and/or designated organizations to analyse the samples.

The results from this genetic research may be reported in a separate report from the CSR or published in scientific journals.

AstraZeneca and its designated organisations may share summary results (such as genetic differences from groups of individuals with a disease) from this genetic research with other researchers, such as Hospitals, Academic Organization or Health Insurance Companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can only use this information for health related research purposes. Researchers may see summary results but they will not be able to see individual patient data or any personal identifiers.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

Statistical Methods and Determination of Sample Size

The number of patients that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A Statistical Analysis Plan will be prepared where appropriate.

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

1. Introduction

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

Specific guidance on managing liver abnormalities can be found in Section 6.3.7 of the protocol.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study.

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

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

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

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

2. Definitions

Potential Hy's Law (PHL)

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

Hy's Law (HL)

AST or ALT ≥3 x ULN **together with** TBL ≥2 x ULN, where no other reason, other than the IP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

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

3. Identification of Potential Hy's Law Cases

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

- ALT ≥3 x ULN
- AST ≥3 x ULN
- TBL ≥2 x ULN

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

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

4. Follow-up

4.1 Potential Hy's Law Criteria not met

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

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

4.2 Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment (See Section 6. Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment)
- Notify the AstraZeneca representative who will then inform the central Study Team

- Within 1 day of PHL criteria being met, the Investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting.

- For patients that met PHL criteria prior to starting IMP, the investigator is not required to submit a PHL SAE unless there is a significant change# in the patient's condition.

The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Complete follow-up SAE form as required.

- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician.

- Complete the three Liver CRF Modules as information becomes available

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

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

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

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

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

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

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF

- If the alternative explanation is an AE/SAE: update the previously submitted Potential Hy's Law SAE and AE CRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AstraZeneca standard processes

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

- Send updated SAE (report term 'Hy's Law') according to AstraZeneca standard processes.

  – The 'Medically Important' serious criterion should be used if no other serious criteria apply

  – As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

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

- Provides any further update to the previously submitted SAE of Potential Hy's Law, (report term now ' Hy's Law Case') ensuring causality assessment is related to IMP and seriousness criteria is medically important, according to CSP process for SAE reporting.

- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

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

This section is applicable to patients with liver metastases who meet PHL criteria on study treatment having previously met PHL criteria at a study visit prior to starting study treatment.

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

  – If there is no significant change no action is required

- If there is a significant change notify the AstraZeneca representative, who will inform the central Study Team, then follow the subsequent process described in 4.2 Potential Hy's Law Criteria met of this Appendix

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

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

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

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

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

- Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study eg, chronic or progressing malignant disease, severe infection or liver disease, or did the patient meet PHL criteria prior to starting study treatment and at their first on study treatment visit as described in section 6. Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment?

If No: follow the process described in section 4.2 Potential Hy's Law Criteria met within this Appendix

If Yes:

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

- If there is no significant change no action is required
- If there is a significant change follow the process described in Section 4.2 of this Appendix

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

References

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

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

Appendix E Acceptable Birth Control Methods

Olaparib is regarded as a compound with medium/high foetal risk.

Women of childbearing potential and their partners, who are sexually active, must agree to the use of TWO highly effective forms of contraception in combination (as listed below). This should be started from the signing of the informed consent and continue throughout the period of taking study treatment and for at least 1 month after last dose of study drug(s), or they must totally/truly abstain from any form of sexual intercourse (see below).

Male patients must use a condom during treatment and for 6 months after the last dose of study drug(s) when having sexual intercourse with a pregnant woman or with a woman of childbearing potential. Female partners of male patients should also use a highly effective form of contraception if they are of childbearing potential (as listed below). Male patients should not donate sperm throughout the period of taking study drug(s) and for 6 months following the last dose of study drug(s).

Acceptable non hormonal birth control methods include:

- Total/True abstinence: When the patient refrains from any form of sexual intercourse and this is in line with their usual and/or preferred lifestyle; this must continue for the total duration of the study and for at least 1 month after the last dose of study drug (for 6 months after last dose for male patients. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods or declaration of abstinence solely for the duration of a study) and withdrawal are not acceptable methods of contraception.

- Vasectomised sexual partner PLUS male condom. With participant assurance that partner received post-vasectomy confirmation of azoospermia.

- Tubal occlusion PLUS male condom

- Intrauterine device PLUS male condom. Provided coils are copper-banded

Acceptable hormonal methods:

- Normal and low dose combined oral pills PLUS male condom

- Cerazette (desogestrel) PLUS male condom. Cerazette is currently the only highly efficacious progesterone based pill.

- Hormonal shot or injection (eg, Depo-Provera) PLUS male condom

- Etonogestrel implants (eg, Implanon, Norplant) PLUS male condom

- Norelgestromin / ethinyl estradiol transdermal system PLUS male condom

- Intrauterine system (IUS) device (eg, levonorgestrel releasing IUS -Mirena®) PLUS male condom

- Intravaginal device (eg, ethinyl estradiol and etonogestrel) PLUS male condom

Appendix F Guidelines for Evaluation of Objective Tumour Response Using RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumours)

1. INTRODUCTION

This appendix details the implementation of RECIST 1.1 Guidelines (Eisenhauer et al 2009) for the D5336C00001 study with regards to Investigator assessment of tumour burden including protocol-specific requirements for this study.

2. DEFINITION OF MEASURABLE, NON MEASURABLE, TARGET AND NON TARGET LESIONS

Only patients with measurable disease at baseline should be included in the study. Measurable disease is defined by the presence of at least one measurable lesion which has not been previously irradiated and not chosen for biopsy during the screening period.

Measurable:

A lesion, not previously irradiated and not chosen for biopsy during the screening period, that can be accurately measured at baseline as ≥ 10 mm in the longest diameter (except lymph nodes which must have short axis ≥ 15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) and which is suitable for accurate repeated measurements. If only one measurable lesion exists, it is acceptable to be used (as a target lesion) as long as it has not been previously irradiated and baseline tumour assessment scans are done at least 14 days after the screening biopsy is performed.

Non measurable:

- All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15mm short axis at baseline*).
- Truly non measurable lesions include the following: bone lesions, leptomeningeal disease, ascites, pleural / pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by CT or MRI.
- Previously irradiated lesions**
- Skin lesions assessed by clinical examination
- Brain metastasis
- Lesions biopsied within the screening period (exception: If only one measurable lesion exists, it is acceptable to be used [as a target lesion] as long as it has not been

previously irradiated and baseline tumour assessment scans are done at least 14 days after the screening biopsy is performed).

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

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

Special Cases:

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

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

Target lesions:

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

Non target lesions:

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline.

3. METHODS OF ASSESSMENT

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

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

App. Table 1 Summary of Methods of Assessment

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

3.1. CT AND MRI

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

In the D5336C00001 study it is recommended that CT examinations of the Chest and abdomen (including liver and adrenal glands), will be used to assess tumour burden at baseline and follow-up visits. CT examination with intravenous (i.v.) contrast media administration is the preferred method. MRI should be used where CT is not feasible or it is medically contra-indicated. For brain lesion assessment, MRI is the preferred method although CT is acceptable.

3.2. CLINICAL EXAMINATION

In the D5336C00001 study, clinical examination will not be used for assessment of TL. Clinically detected lesions can be selected as target lesions if they are assessed by CT or MRI scans. Clinical examination can be used to assess NTL and to identify the presence of new lesions.

3.3. X-RAY

3.3.1. Chest X-ray

In the D5336C00001 study, chest x-ray assessment will not be used for assessment of TL as they will be assessed by CT examination or MRI examination. Chest X-ray can, however, be used to assess NTL and to identify the presence of new lesions.

3.3.2. Plain X-ray

In the D5336C00001 study plain x-ray may be used as a method of assessment for bone NTL and to identify the presence of new bone lesions.

3.4. ULTRASOUND

In the D5336C00001 study, ultrasound examination will not be used for assessment of TL and NTL as it is not a reproducible method, does not provide an accurate assessment of tumour size and it is subjective and operator dependent. Ultrasound examination can, however, be used to identify the presence of new lesions. If new clinical symptoms occur and an ultrasound is performed then new lesions should be confirmed by CT or MRI examination.

3.5. ENDOSCOPY AND LAPAROSCOPY

In the D5336C00001 study, endoscopy and laparoscopy will not be used for tumour assessments as they are not validated in the context of tumour assessment.

3.6. TUMOUR MARKERS

In the D5336C00001 study, tumour markers will not be used for tumour response assessments as per RECIST 1.1.

3.7. CYTOLOGY AND HISTOLOGY

In the D5336C00001 study, histology will not be used as part of the tumour response assessment as per RECIST 1.1.

Cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment is required when the measurable tumour has met criteria for response or stable disease. In such circumstances, the cytology is necessary to differentiate between response / stable disease (an effusion may be a side effect of the treatment) and progressive disease (if the neoplastic origin of the fluid is confirmed). Where cytology findings are not available, any effusion that significantly worsens (from trace to large) or appearance of clinically significant effusion (requiring change in drug therapy) during the study treatment will be considered to be progression of NTL, or disease progression due to new lesions.

3.8. ISOTOPIC BONE SCAN

Bone lesions identified on an isotopic bone scan at baseline and confirmed by CT, MRI or X-ray at baseline should be recorded as NTL and followed by the same method as per baseline assessment.

In the D5336C00001 study, isotopic bone scans may be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. New lesions will be recorded where a positive hot-spot that was not present on the baseline bone scan assessment is identified on a bone scan performed at any time during the study. The Investigator should consider the positive hot-spot to be a significant new site of malignant disease and represent true disease progression in order to record the new lesion. Confirmation by CT, MRI and x-ray is recommended where bone scan findings are equivocal.

3.9 FDG-PET SCAN

In the D5336C00001 study, FDG-PET scans may be used as a method for identifying new lesions, according with the following algorithm: New lesions will be recorded where there is positive FDG uptake* not present on baseline FDG-PET scan or in a location corresponding to a new lesion on CT/MRI at the same follow-up visit. If there is no baseline FDG-PET scan available, and no evidence of new lesions on CT/MRI scans then follow-up CT/MRI assessments should be continued, scheduled as per protocol or clinical indicated, in order to confirm new lesions.

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

4. TUMOUR RESPONSE EVALUATION

4.1. SCHEDULE OF EVALUATION

Baseline assessments should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients and should be performed no more than 28 days before the start of study treatment (refer to Study Plan and Section 4.1 from the study protocol). Follow-up assessments will be performed every 8 weeks (± 1 week) for the first 72 weeks and every 12 weeks (± 1 week) thereafter, after randomisation until objective disease progression as defined by RECIST 1.1 even if a patient discontinues treatment prior to progression or receives other anti-cancer treatment. Any other sites at which new disease is suspected should also be adequately imaged at follow-up.

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

4.2 TARGET LESIONS (TL)

4.2.1 Documentation of target lesions

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

The site and location of each TL should be documented as well as the longest diameter for non nodal lesions (or short axis for lymph nodes). All measurements should be recorded in

millimeters. At baseline the sum of the diameters for all TL will be calculated and reported as the baseline sum of diameters. At follow-up visits the sum of diameters for all TL will be calculated and reported as the follow-up sum of diameters.

Special cases:

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

4.2.2 Evaluation of target lesions

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

App. Table 2 Evaluation of target lesions

Complete Response (CR)	Disappearance of all target lesions since baseline. Any pathological lymph nodes selected as target lesions must have a reduction in short axis to < 10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of TL, taking as reference the baseline sum of diameters
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5mm.
Not Evaluable (NE)	Only relevant if any of the target lesions were not assessed or not evaluable or had a lesion intervention at this visit. Note: If the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a target lesion response

4.3 NON TARGET LESIONS (NTL)

4.3.1 Evaluation of non target lesions

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

App. Table 3 Evaluation of Non Target Lesions

Complete Response (CR)	Disappearance of all non target lesions since baseline. All lymph nodes must be non pathological in size (< 10 mm short axis).
Non CR/Non PD	Persistence of one or more NTL
Progression (PD)	Unequivocal progression of existing non target lesions. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
Not Evaluable (NE)	Only relevant when one or some of the non target lesions were not assessed and, in the Investigator's opinion, they are not able to provide an evaluable overall non target lesion assessment at this visit. Note: For patients without target lesions at baseline, this is relevant if any of the non target lesions were not assessed at this visit and the progression criteria have not been met.

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

4.4 NEW LESIONS

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: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour.

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

4.5 SYMPTOMATIC DETERIORATION

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

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

4.6 EVALUATION OF OVERALL VISIT RESPONSE

The overall visit response will be derived using the algorithm shown in Table 4.

App. Table 4 Overall Visit Response

Target lesions	Non Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	NA	No	CR
CR	Non CR/Non PD	No	PR
CR	NE	No	PR
PR	Non PD or NE	No	PR
SD	Non PD or NE	No	SD
NE	Non PD or NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable, NA = not applicable (only relevant if there were no NTLs at baseline).

5. CENTRAL REVIEW

The Contract Research Organisation (CRO) appointed by AstraZeneca to perform the independent central review for this study will provide specification for radiological imaging protocols in standard acquisition guidelines documentation.

6. REFERENCES

Eisenhauer et al 2009
Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 45 (2009) 228-247.

Appendix G ECOG Performance Status

These scales and criteria are used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. They are included here for health care professionals to access.

ECOG PERFORMANCE STATUS*

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982

Appendix H Not applicable following CSPv6.0 provided there has been a minimum washout period of 10 days since the final dose of AZD1775: Disallowed Medications and Medications to be Administered with Caution

DISALLOWED MEDICATIONS AND MEDICATIONS TO BE ADMINISTERED WITH CAUTION

Formal drug-drug interaction studies have not yet been performed with AZD1775, therefore, the potential for drug-drug interaction described in this protocol are based on findings from *in vitro* studies and clinical experience.

In vitro data has shown that AZD1775 is metabolised predominantly by CYP3A4, with an FMO3 and/or FMO5 component. As a result, there is potential for the exposure of AZD1775 to be affected by drugs which inhibit or induce the metabolism of CYP3A4. In the clinic, co-administration of AZD1775 with the moderate CYP3A4 inhibitor, aprepitant, resulted in a 40% increase in the plasma levels of AZD1775. Drugs known to be moderate to strong inhibitors/inducers of CYP3A4 are therefore prohibited for use in the current study, including aprepitant.

In vitro data suggests that AZD1775 may be a weak reversible inhibitor of CYP2C19 (IC50 12μM). Caution should therefore be exercised when AZD1775 is co-administered with agents that are sensitive substrates of CYP2C19, or substrates of this enzyme with a narrow therapeutic range.

Based on *in vitro* studies, AZD1775 has been shown to be a weak reversible inhibitor (IC50 14μM) and a time-dependent inhibitor of CYP3A4 (Kinact 0.061/min, Ki 6.04 μM). The full impact of the time dependent inhibition is currently unknown, however, modelling data has predicted an 8-10 fold increase in the exposure of sensitive CYP3A4 substrates when administered with AZD1775 (250 mg BID for 5 doses). To date, no significant DDI effects have been reported in the clinic that may be related to the TDI finding. However, sensitive CYP3A4 substrates or substrates of CYP3A4 with a narrow therapeutic window are prohibited.

AZD1775 has been shown to be a weak inducer of CYP1A2 *in vitro* (39% increase in activity of positive control). Given the nature of the AZD1775 dosing schedule, however, the risk of induction in the clinic is considered low. No specific precautions are recommended at this time, except to be initially vigilant when using substrates of CYP1A2 with a narrow therapeutic range.

Transporter studies (*in vitro*) have shown that AZD1775 is both a substrate and inhibitor (IC_{50} 20 μM) of P-gp. Maximum impact of these finding is likely to occur for drugs administered orally at the same time as AZD1775. Caution should therefore be exercised when agents that are inhibitors or substrates of P-gp are administered concomitantly with AZD1775.

Recent *in vitro* transporter studies have shown AZD1775 to be an inhibitor of BCRP (IC_{50} 5.1 μM). This finding is particularly relevant for drugs administered orally where exposure is normally limited by BCRP-mediated efflux, in particular some statins such as rosuvastatin. Other drugs where the disposition is mediated via BCRP should be administered with caution, dose modification considered or substituted by an alternative drug.

Use of metformin should be used with caution in this study as recent *in vitro* transporter data have shown AZD1775 is an inhibitor of Multidrug and Toxin Extruder 1 (MATE1) and MATE2K.

Caution should be used when administering drugs that are substrates of these transporters (eg, cimetidine, acyclovir, fexofenadine) as the clinical relevance of AZD1775 inhibition of the MATE pathway is not known in these compounds.

Herbal preparations/medications can be substrates, inhibitors and inducers, similar to any registered medication. Herbal preparations are therefore not allowed throughout the study. These herbal medications include, but are not limited to: St. John's wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng.

In addition, any other drugs should be avoided at the Investigator's discretion if, in their opinion, the co-administration with AZD1775 may increase the risk of a clinically significant drug interaction.

A list of the main CYP3A4 substrates, inhibitors (strong and moderate) and inducers, CYP2C19 substrates, P-gp substrates, and inhibitors and BCRP substrates is shown below. This is not an exhaustive list and further details can be found at Expert Opin Drug Metab Toxicol (2013) 9(6):737-751.

CYP3A4 Inhibitors

Strong

- Boceprevir
- Clarithromycin
- Cobicistat (GS-9350)
- Conivaptan
- Danoprevir
- Elvitegravir
- Fosamprenavir
- Grapefruit juice
- Idelalisib
- Indinavir
- Itraconazole
- Ketoconazole
- LCL161
- Lopinavir
- Mibefradil
- Nefazodone
- Nelfinavir
- Posaconazole
- Ritonavir
- Saquinavir
- Telaprevir
- Telithromycin
- Tipranavir
- Troleandomycin
- Voriconazole

Moderate

- ACT-178882
- Amprenavir
- Aprepitant
- Atazanavir
- Casopitant
- Ciprofloxacin
- Crizotinib
- Darunavir
- Dronedarone
- Diltiazem
- Erythromycin
- FK1706
- Fluconazole
- Fosamprenavir
- Imatinib
- Ledipasvir
- Lomitapide
- Netupitant
- Schisandra sphenanthera
- Tofisopam
- Verapamil

Weak

Almorexant
Alprazolam
AMD070
Amiodarone
Amlodipine
Atorvastatin
Azithromycin
Berberine
Bicalutamide
Blueberry juice
Chlorzoxazone
Cilostazol
Cimetidine
Clotrimazole
Cranberry juice
Cyclosporine
Daclatasvir
Delavirdine
Everolimus
Faldaprevir
Fluvoxamine
Fosaprepitant (IV)
Ginkgo
Goldenseal
GSK1292263
GSK2248761
Isoniazid
Ivacaftor
Lacidipine
I Linagliptin
Lomitapide
M100240
Nilotinib
Oral contraceptives
Pazopanib
Peppermint oil
Propiverine
Ranitidine
Ranolazine
Resveratrol
Roxithromycin
Seville orange juice
Simeprevir
Sitaxentan
Suvorexant
Tabimorelin
Tacrolimus
Teriflunomide
Ticagrelor
Tipranavir/ritonavir
Tolvaptan
Zileuton

CYP3A4 Inducers (Strong and Moderate)

Avasimibe
Bosentan
Carbamazepine
Efavirenz
Enzalutamide
Etravirine
Genistein
Lersivirine
Lopinavir
Mitotane
Modafinil
Nafcillin
Phenobarbital
Phenytoin
Rifabutin
Rifampin
Ritonavir
Semagacestat
St John's Wort
Thioridazine
Tipranavir

CYP3A4 Inducers (Weak)

Amprenavir
Aprepitant
Armodafinil
AZD 7325
Bexarotene
Boceprevir
Brivaracetam
Clobazam
Danshen
Dexamethasone
Echinacea
Eslicarbazepine
Garlic
Gingko
Ginseng
Glycyrrhizin
LCL161
Methylprednisolone
Nevirapine
Oritavancin
Oxcarbazepine
PA-824
Pleconaril
Prednisone
Quercetin
Raltegravir
Ritonavir
Rufinamide
Sorafenib
Stribild
Telaprevir
Terbinafine
Ticagrelor
Ticlopidine
Topiramate
Troglitazone
Vemurafenib
Vicriviroc and ritonavir
Vinblastine

CYP3A and CYP3A4 Sensitive Substrates or Substrates with a Narrow Therapeutic Range

ABT-384
Alfentanil
Aprepitant
Alfuzosin
Almorexant
Alpha-Dihydroergocryptine
Amiodarone
Aplaviroc
Aprepitant
Astemizole
Atazanavir
Atorvastatin
Avanafil
Bexarotine
BIRL 355
Bortezomib
Bosutinib
Brecanavir
Brotizolam
Budesonide
Buspirone
Capravirine
Carbamazepine
Casopitant
Cisapride,
Conivaptan
Cyclophosphamide
Cyclosporine
Danoprevir
Darifenacin
Darunavir
Dasatinib
Dihydroergotamine
Disopyramide
Dronedarone
Docetaxol
Dofetilide
Doxorubicin
Ebastine
Eletriptan
Elvitegravir
Eplerenone
Ergotamine
Erlotinib
Etoposide
Everolimus
Felodipine
Fentanyl
Fluticasone
Gefitinib
Halofantrine
Ibrutinib
Ifosfamide
Imatinib
Indinavir
Ironotecan
Ivacaftor
Ixabepilone
L-771,688
Lapatinib
Levomethadyl (LAAm)
Lomitapide
Lopinavir
Lovastatin
Lurasidone
Maraviroc,
Midazolam
Midostaurin
Mosapride
Neratinib
Nilotinib
Nisoldipine
Paclitaxel
Pazopanib
Perospirone
Pimozide
Propafenone
Propofol
Quetiapine
Quinidine
Ranolazine
Ridaforolimus
Romidepsin
Saquinavir
Sildenafil
Simeprevir
Simvastatin
Sirolimus
Tacrolimus
Temsirolimus
Terfenadine
Ticagrelor
Theoophylline
Thioridazine
Thiotepa
Tilidine
Tipranavir
Tolvaptan
Triazolam
Tretinoin
Ulipristal
Vardenafil
Vicriviroc
Voclosporin

CYP2C19 Sensitive Substrates or Substrates with a Narrow Therapeutic Range

Diazepam
Gliclazide
Lansoprazole
(R)-Lansoprazole
(S)-Lansoprazole
(S)-Mephenytoin
(R)-Mephobarbital
Omeprazole
(R)-Omeprazole
Pantoprazole
(+)-Pantoprazole
Rabeprazole
Tilidine

CYP1A2 Sensitive Substrates or Substrates with a Narrow Therapeutic Range

Alosetron
Caffeine
Duloxetine
Melatonin
Ramelteon
Tacrine
Theophylline
Tizanidine

P-gp Substrates

Colchicine
Digoxin
Fexofenadine
Indinavir
Paclitaxel
Topotecan
Vincristine

If a patient requires initiation of digoxin during the study, or is already receiving treatment with digoxin, monitoring of digoxin levels is recommended according to local practice (as the levels of digoxin may increase). Monitoring of digoxin levels is also recommended when the patient has completed dosing with study treatment (as the levels of digoxin may then decrease).

P-gp Inhibitors (Strong)

Cyclosporine
Elacridar
Erythromycin
Itraconazole
Ketoconazole
LY335979Quinidine
Ritonavir
Valspodar
Verapamil

BCRP Substrates

Daunorubicin
Doxorubicin
Rosuvastatin
Sulfasalazine
Topotecan

Appendix I Ceralasertib Guidelines for Potential Interactions with Concomitant Medications

Ceralasertib is an investigational drug for which no data on *in vivo* interactions are currently available. Potential interaction is considered on the basis of preclinical *in vitro* data only.

The lists of CYP and transporter inhibitors/inducers, and CYP and transporter substrates are available in below. They are not exhaustive and the absence of a drug from these lists does not imply that its combination with ceralasertib is safe. If ceralasertib is being administered in combination, potential interactions of the combination partner should also be considered.

Restrictions regarding drugs affection CYP metabolism

There are currently no data confirming that there is a pharmacokinetic (PK) interaction between these agents and ceralasertib; a potential interaction is considered on the basis of preclinical and *in vitro* data only. ceralasertib is predominantly eliminated via CYP3A metabolism, therefore CYP3A inhibitors or inducers may increase or decrease exposure to ceralasertib, respectively. Potent inhibitors or inducers of CYP3A should not be combined with ceralasertib. In vitro data also suggest that ceralasertib may be metabolised by CYP2A8 but a lesser extent, therefore caution should be applied with co administration of potent inhibitors or inducers of CYP2C8.

These lists are not intended to be exhaustive, and similar restrictions will apply to other agents that are known to modulate CYP3A activity or CYP2C8. Please contact AstraZeneca with any queries you have on this issue. Please refer to full prescribing information for all drugs prior to co-administration with ceralasertib.

App. Table 5: Drugs known to be inhibitors and inducers of CYP3A

Potent CYP3A inhibitors	Potent CYP3A inducers
boceprevir	apalutamide
ceritinib	avasimibe
clarithromycin	carbamazepine
cobicistat (GS-9350)	enzalutamide
conivaptan	ivosidenib
danoprevir / RIT	lumacaftor
elvitegravir / RIT	mitotane
grapefruit juice[2]	phenobarbital
idelalisib	phenytoin
indinavir	rifampin
indinavir /RIT	rifapentine
itraconazole	St John's Wort extract
ketoconazole	
LCL161	
lopinavir / RIT	
mibefradil	
mifepristone	
nefazodone	
nelfinavir	
posaconazole	
ribociclib	
ritonavir	
saquinavir	
saquinavir / RIT	
telaprevir	
telithromycin	
tipranavir/RIT	
troleandomycin	
VIEKIRA PAK2[1]	
voriconazole	

List created using the University of Washington Drug-Drug Interaction Database Jan 2012.

RIT=Ritonivir. Ritonavir has dual effects of simultaneous CYP3A inhibition and induction, and the net pharmacokinetic outcome during chronic ritonavir therapy is inhibition of CYP3A activity

[1] VIEKIRA PAK = 150/100 mg paritaprevir/ritonavir + 25 mg ombitasvir + 800 mg dasabuvir for 28 days. [2]. Double-strength grapefruit juice. Patients should abstain from eating large amounts of grapefruit and Seville oranges (and other products containing these fruits e.g., grapefruit juice or marmalade) during the study (e.g., no more than a small glass of grapefruit juice (120 mL) or half a grapefruit or 1-2 teaspoons (15 g) of Seville orange marmalade daily

App. Table 6: Drugs known to be inhibitors and inducers of CYP2C8

Potent CYP2C8 inhibitors	Potent CYP2C8 inducers
gemfibrozil clopidogrel	None identified

List created using the University of Washington Drug-Drug Interaction Database Jan 2020.

Drugs known to be inhibitors or inducers of Pgp and/or BCRP, undertake appropriate monitoring if coadministration is necessary

Ceralasertib is a substrate of Pgp and BCRP. Co-administration of Pgp inhibitors/inducers or BCRP inhibitors/inducers may affect exposure to ceralasertib therefore it is recommended that these are not co-administered with ceralasertib.

These lists are not intended to be exhaustive, and similar restrictions will apply to other agents that are known to modulate Pgp activity or BCRP activity. Please contact AstraZeneca with any queries you have on this issue. Please refer to full prescribing information for all drugs prior to co-administration with ceralasertib.

App. Table 7: Drugs known to be inhibitors or inducers of P-gp

Drugs Known to be Inhibitors of Pgp[a]	Drugs Known to be Inducers of Pgp[b]
Amiodarone azithromycin captopril carvedilol clarithromycin conivaptan cremophor curcumin diltiazem dronedarone elacridar erythromycin felodipine fluvoxamine ginkgo indinavir itraconazole ketoconazole lapatinib lopinavir and ritonivir mibefradil milk thistle mirabegron nelfinavir nifedipine nitrendipine paroxetine quercetin quinidine ranolazine rifampin ritonavir saquinavir/ritonavir schisandra chinensis extract St Johns Wort talinolol telaprevir telmisartan ticagrelor tipranavir/ritonavir tolvaptan valspodar (PSC 833) verapamil	avasimibe carbamazepine efavirenz genistein phenytoin rifampin St Johns Wort

a. Inhibitors listed for P-gp are those that showed >25% increase in exposure to a P-gp substrate (e.g. digoxin).

b. Inducers listed for Pgp are those that showed >20 % decrease in exposure to a P-gp substrate (e.g. digoxin)

App. Table 8: Drugs known to be inhibitors or inducers of BCRP

Drugs Known to be Inhibitors of BCRP	Drugs Known to be inducers of BCRP
Afatinib Aripiprazole Curcumin Cyclosporine Elacridar Erlotinib Fluvastatin Fumitremorgin Gefitinib Ivermectin Lapatinib Nilotinib Novobiocin Pantoprazole Pitavastatin Ponatinib Quercetin Quizartinib Rabeprazole Regorafenib Rilpivirine Sulfasalazine Sunitinib Tacrolimus Teriflunomide Trametinib Trifluoperazine Vismodegib eltrombopag Atazanavir Lopinavir Ritonavir Tipranavir Omeprazole Estrone 17b-estradiol Imatinib mesylate	Please check individual drugs on a case by case basis

List created using http://dmd.aspetjournals.org/content/dmd/43/4/490.full.pdf

Note: Although BCRP is involved in a number of clinically relevant DDIs, none of the cited inhibitors above is truly specific for this transporter

Drugs known to be substrates of CYP3A4 and/or CYP2B6, undertake appropriate monitoring if coadministration is necessary

Ceralasertib is a potential inducer of CYP3A4 and CYP2B6. Therefore caution should be applied with co administration of drugs that are either completely metabolised by CYP3A4 and/or CYP2B6, or that are substrates of CYP3A4 and/or CYP2B6 and also have a narrow therapeutic index. Investigators should be aware that the exposure of other drugs metabolised by CYP3A4 and/or CYP2B6 may be reduced.

App. Table 9: Drugs known to be metabolised by CYP3A4 and have a narrow therapeutic index

Alfentanil
Cyclosporine
Dihydroergotamine
Ergotamine
Fentanyl
Pimozide
Quinidine
Sirolimus
Tacrolimus
Astemizole
Cisapride
Terfenadine

App. Table 10: Drugs known to be metabolised by CYP2B6 and have a narrow therapeutic index

Cyclophosphoamide
Ifosfamide
Efavirenz
Bupropion
Propofol
Thiotepa
Sorafenib
alfentanil
ketamine
methadone
methoxetamine
nevirapine
propofol
selegiline
sertraline
sorafenib
tamoxifen
valproic acid

From Flockhart DA (2007). "Drug Interactions: Cytochrome P450 Drug Interaction Table". Indiana University School of Medicine

Drugs known to be substrates of OATP1B1 and BCRP, undertake appropriate monitoring if coadministration is necessary

Ceralasertib is also an inhibitor of OATP1B1 and BCRP. Caution should be applied with coadministration of substrates of OATP1B1 and/or BCRP as ceralasertib may increase their exposure.

These lists are not intended to be exhaustive and appropriate medical judgment is required. Please contact AstraZeneca with any queries you have on this issue. Please refer to full prescribing information for all drugs prior to co-administration with ceralasertib.

App. Table 11: Drugs known to be substrates of OATP1B1

Atorvastatin
Fluvastatin
Lovastatin
Pitavastatin
Pravastatin
Rosuvastatin
Simvastatin
Ezemibe
Simvastatin
Methotrexate
Rifampin
Bosentan
Glyburide
Repaglinide
Valsartan
Olmesartan
Atrasentan

List created using https://www.solvobiotech.com/transporters/OATP1B1

App. Table 12: Drugs known to be substrates of BCRP

Anthracyclines
Daunorubicin
Doxorubicin
Topotecan
SN-38
Irinotecan
Methotrexate
Imatinib
Irinotecan
Mitoxantrone
nucleoside analogs
prazosin
pantoprazole
topotecan
rosuvastatin and other statins
teriflunomide
chlorothiazide

List created using https://www.solvobiotech.com/transporters/bcrp

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