AstraZeneca

Clinical Study Protocol

Drug Substance	cediranib (AZD2171) plus olaparib (AZD2281)
Study Code	D8488C00001
Edition Number	5.0
Date	15 Jan 2019

A single arm, open-label, Phase IIb study to assess the efficacy and safety of the combination of cediranib and olaparib tablets in women with recurrent platinum resistant epithelial ovarian cancer, including fallopian tube and/or primary peritoneal cancer who do not carry a deleterious or suspected deleterious germline *BRCA* mutation

VERSION HISTORY

Version 5.0, 15 Jan 2019
Changes to the protocol are summarised below:

- The sample size has been reduced from 100 to approximately 60 patients (Sections 1.4 and 8.2). Consequential changes for clarity have been made in multiple sections throughout the protocol.

Rationale for change

Slower than projected recruitment due to emerging availability and uptake of Polyadenosine 5'diphosphoribose (poly [ADP ribose]) polymerization (PARP) inhibitors in earlier lines of treatment while patients are still platinum sensitive, diminishing the intended study population available for recruitment for this treatment.

- The analysis for overall survival (OS) will now occur at the primary analysis, ie, 8 months after the last subject has started treatment (see Section 1.4 [Figure 2] and schedule of study assessments in Section 4 [Table 5]). Consequential changes for clarity have been made in multiple sections throughout the protocol.

Rationale for change

To reflect revised study timelines.

- Addition of a Final Protocol Visit (FPV) (Section 4.4). The FPV applies to patients continuing to receive clinical benefit without meeting any discontinuation criteria during the study and will occur at their last scheduled visit prior to primary data cut-off, focussed on capturing safety information (see Section 4 [Table 5, footnote 'a']). Consequential changes for clarity have been made in multiple sections throughout the protocol.

Rationale for change

To allow safety assessment/monitoring before primary data cut-off, for patients that are continuing to receive clinical benefit from study treatment.

- Update to Section 4.5, End of Study.

Rationale for change

Clarification of end of study procedures due to addition of a FPV for patients continuing to receive clinical benefit without meeting any discontinuation criteria during the study.

- Update to requirements for targeted safety questionnaires (Section 6.3.4).

Rationale for change

To reflect the current list of the topics requiring specific safety data collection for investigational products.

- Response rates and associated 95% CIs for a sample of 60 added (Section 8.2).

Rationale for change

To reflect new sample size of approximately 60 patients.

- Addition of guidance regarding confirmed myelodysplastic syndrome (MDS) or other clonal blood disorder (Section 6.8.1.3).

Rationale for change

To align with olaparib standard protocol template.

- Other updates to align with olaparib standard protocol template (Sections 3.8, 5.2.5.1, and 7.7).
- Signatories updated (Appendix A)
- Other minor editorial changes throughout (corrections to spelling mistakes, formatting, etc.).
- Revision to Appendix F to clarify that confirmation of progressive disease is not mandated in this study

Version 4.0, 06 Sep 2017
Changes to the protocol are summarised below:

Figure 2 Study flow chart

This flow chart has been amended to indicate that prior-antiangiogenic is optional and to indicate that a futility analysis will be performed after 20 evaluable patients.

Section 3.1 Inclusion criterion #4

Old text

4. Recurrent platinum-resistant disease, defined as disease progression within 6 months of the last receipt of platinum-based chemotherapy.

    - Patients with platinum refractory disease defined as disease progression during the last receipt of platinum-based therapy, are not eligible

- Patients with primary platinum resistant/refractory disease defined as progression during or within 6 months of completing first-line platinum-based chemotherapy are not eligible.

New text

4. Recurrent platinum-resistant disease, defined as disease progression within 6 months **(182 days)** of the last receipt of platinum-based chemotherapy.

- Patients with platinum refractory disease defined as disease progression during the last receipt of platinum-based therapy, are not eligible

- Patients with primary platinum resistant/refractory disease defined as progression during or within 6 months **(182 days)** of completing first-line platinum-based chemotherapy are not eligible.

Rationale for change:

To clarify the length of time for disease progression by adding duration in days

Section 3.1 Inclusion criterion #8

Old text

8. Prior receipt of antiangiogenic treatment including but not limited to bevacizumab in first line or recurrent setting

New text

8. Prior receipt of antiangiogenic treatment, including but not limited to bevacizumab, is optional. If used, it can be in the first line or recurrent setting.

Rationale for change:

Bevacizumab has recently been approved by FDA for patients with recurrent ovarian cancer. Despite being an available treatment option in US, feasibility data show that nearly half of the recurrent ovarian cancer patients particularly in earlier lines of treatment do not receive bevacizumab. Therefore, to enable recruitment, prior receipt of antiangiogenic treatment is now changed from mandatory to optional.

Section 3.1 Inclusion criterion #9

Old text

9. At least 3 prior lines of chemotherapy for advanced ovarian cancer are required

- Up to 2 prior non-platinum chemotherapy regimens are allowed but not required

– Hormonal therapy (such as tamoxifen, aromatase inhibitors), bevacizumab or other immunotherapy used as a single agent will not count as a line of chemotherapy

New text

9. At least 3 prior lines of **therapy** for advanced ovarian cancer as follows:

– **Platinum chemotherapy: at least two prior lines required**

– **Non-platinum chemotherapy: up to two prior lines are allowed but not required**
– Hormonal therapy (such as tamoxifen, aromatase inhibitors), bevacizumab or other immunotherapy used as a single agent will not count as a line of therapy

Rationale for change:

To clarify what treatments will count towards prior lines of therapy.

Section 3.10.2 – Survival status for withdrawn consent and lost to follow up patients

At the time of OS analysis, the survival status of all patients in the full analysis set should be re-checked, this includes those patients who withdrew consent or are classified as "lost to follow up."

- Lost to follow up – site personnel should check hospital records, the patients' current physician, and a publicly available death registry (if available) to obtain a current survival status in the 2 weeks following data cut-off. (The SURVIVE module will be updated.)

- In the event that the patient has actively withdrawn consent to the processing of their personal data, the survival status of the patient can be obtained by site personnel from publicly available death registries or resources (if available) where it is possible to do so under applicable local laws to obtain a current survival status in the 2 weeks following data cut-off. (The SURVIVE module will be updated.)

Rationale:

This new section has been created to clarify that at the time of OS analysis, site personnel should attempt to obtain the survival status for all patients in the full analysis set who had previously withdrawn consent or were considered lost to follow-up using publicly available resources where available.

Table 5 Schedule of study assessments

Screening visit window corrected to Day -28 to -1 and treatment start corrected to Day 1.

In addition, minor administrative corrections have been made throughout the protocol and are not detailed here further.

Version 3.0, 28 March 2017
Changes to the protocol are summarised below:

There are several Editorial changes to align the protocol with the new AstraZeneca Protocol Template, which include minor changes to section headings. The significant changes are listed below:

Executive Summary. The number of sites has been increased to 40 (from 20) and the start and estimated end date have been amended to align with the current status of the study.

Section 1.5 Study governance and oversight

Old text

6.8 Study governance and oversight

The patient safety data from the study will be closely monitored on an ongoing basis by the Sponsor and a Study Steering Committee. Issues identified will be addressed; for instance, this could involve amendments to the study protocol and letters to Investigators.

In this Phase IIb study, a Data Monitoring Committee was not considered necessary as it is an open label study and the safety profiles of olaparib and cediranib as monotherapies and in combination, have previously been established.

New text
1.5 Study governance and oversight

The patient safety data from the study will be closely monitored on an ongoing basis by the Sponsor and a Study Steering Committee. Issues identified will be addressed; for instance, this could involve amendments to the study protocol and letters to Investigators.

1.5.1 Steering Committee

The Steering Committee will consist of two investigators (including the Principal Investigator) and AZ representatives including clinician, statistician and clinical scientist. The remit is to review the outcomes of the planned analyses conducted during the trial including the futility analysis, primary analysis and final OS analysis. In addition, safety

topics can be reviewed as needed. The steering committee's remit is to provide an agreed strategic direction for the study.

1.5.2 Data Monitoring Committee

In this Phase IIb study, a Data Monitoring Committee was not considered necessary as it is an open label study and the safety profiles of olaparib and cediranib as monotherapies and in combination, have previously been established.

Rationale for change:

This section has been added, per AstraZeneca new Protocol Template. This was previously covered in Section 6.8 Study governance and oversight – which has been removed. The Section has been expanded to include further details on the structure and functioning of the steering committee.

Section 3.1 Inclusion criteria #4
Old Text

4. Recurrent platinum-resistant disease, defined as radiological evidence of disease recurrence within 6 months of the last receipt of platinum-based chemotherapy. Patients with platinum-refractory disease are not eligible.

New text

4. Recurrent platinum-resistant disease, defined as **disease progression** within 6 months of the last receipt of platinum-based chemotherapy.

   - Patients with platinum refractory disease **defined as disease progression during the last receipt of platinum-based therapy**, are not eligible
   - **Patients with primary platinum resistant/refractory disease defined as progression during or within 6 months of completing first-line platinum-based chemotherapy are not eligible.**

Rationale for the change:

To allow clinical judgement by the investigator as per standard clinical practice without changing the definition of platinum resistant disease, the stipulation for radiological evidence of disease progression is removed. Previous criteria required radiological evidence of platinum-resistant disease which was dependent on when the CT scan was taken rather than on investigator's clinical judgement of when disease progression occurred within the 6-months of the last receipt of platinum-based chemotherapy. The GCIG criteria for platinum resistant ovarian cancer does not stipulate the requirement for radiological evidence of disease progression with 6 months of completing platinum-based chemotherapy (Friedlander M et al 2011, Int J Gynecol Cancer 2011: 21: 771-775). The amendment will

allow enrollment of patients in the study, if judged by the investigator to carry platinum-resistant disease, who otherwise may not have been eligible for the study.

Section 3.1 Inclusion criterion # 8

Old text

5. Prior receipt of antiangiogenic treatment eg, bevacizumab in first line or recurrent setting

New text

5. Prior receipt of antiangiogenic treatment **including but not limited to** bevacizumab in the first line or recurrent setting

Clarification:

Text revised to clarify that prior antiangiogenic treatment is not limited to bevacizumab only.

Section 3.1 Inclusion Criteria #9

Old Text

9. At least three prior lines of chemotherapy for advanced ovarian cancer. Only one prior non-platinum treatment is allowed. Hormonal therapies used as single agents (ie, tamoxifen, aromatase inhibitors) will not count towards this line limit.

New Text

9. At least three prior lines of chemotherapy for advanced ovarian cancer are required.

    - **Up to two** prior non-platinum chemotherapy regimens are allowed **but not required.**
    - Hormonal therapy (such as tamoxifen, aromatase inhibitors), **bevacizumab (or other angiogenesis inhibitor), or other immunotherapy** used as a single agent will not count as a line of chemotherapy.

Rationale for the change:

The allowance of only one prior non-platinum regimen aimed to select patients who start study treatment as soon as platinum resistant relapse is diagnosed. However, in the heavily pre-treated setting of at least 3 prior lines of chemotherapy, it becomes too restrictive.

Therefore, given the high unmet medical need, and considering no significant adverse impact on the study outcome, the criteria has been relaxed to enable recruitment.

Section 3.1 Inclusion criterion # 11

Old text

- Urine protein:creatinine ratio (UPC) ≤1 OR ≤2+ proteinuria on two consecutive dipsticks taken no less than 1 week apart. Patients with 2+ proteinuria on dipstick must also have UPC <0.5 on 2 consecutive samples.

New text:

- Urine protein:creatinine ratio (UPC) ≤1 OR **proteinuria** ≤2+ on two consecutive dipsticks taken no less than 1 week apart. Patients with 2+ proteinuria on dipstick must also have UPC <0.5 on 2 consecutive samples.

Rationale for the change

Text is revised in Table 5 (footnote 'n') to clarify that 2+ refers to proteinuria and not to UPC.

Section 3.8 Restrictions; Section 4:/Table 5 and footnote 'k'; Section 5.2.5.1 Serum or urine pregnancy test; Section 6.6.1 Maternal exposure

Rational for change

Sections have been updated to reflect the new guidance from the Olaparib IB edition 14 which requires regular pregnancy test during olaparib treatment for fertile women of childbearing potential.

Section 4 Table 5

Clarification

The row header 'dipstick' has been revised to 'urinalysis' for clarification.

Correction

Footnote 'i' has been corrected to state that blood pressure should be measured at the clinic every 4 weeks, after Wk 8.

Section 5.3.1.2 PRO-CTCAE

Old text

The following 6 PRO-CTCAE AEs will be collected in the study: nausea, vomiting, diarrhea, decreased appetite, fatigue, and dizziness.

New text

The following 6 PRO-CTCAE AEs will be collected in the study: nausea, vomiting, diarrhea, decreased appetite, fatigue, and dizziness. **In addition to these items from the PRO-CTCAE item bank, the following additional item will be asked together with the PRO-CTCAE items: "In the last 7 days, how much did LOOSE OR WATERY STOOLS (DIARRHEA) INTERFERE with your usual or daily activities?"**

Rationale for the change

Data collection has been amended to include an additional question to a pre-existing question on Diarrhea in the instrument PRO-CTCAE, and to the ERT logpad. The rationale for this is that the item 'Diarrhea' was earlier assessed only on one dimension 'frequency'. The addition of the new question will allow the assessment on two dimensions (frequency and interference). Although interference is not a standard NCI PRO-CTCAE item for diarrhoea, NCI accepts that individual sponsors can add dimensions to those in the item bank. Diarrhoea is a very common AE for cediranib and assessing the impact of the adverse event on patient well-being is clinically relevant. Furthermore, diarrhoea is reported as a very common event for olaparib, therefore assessing the impact of the combination on frequency and interference is important.

Section 6.4 Reporting of serious adverse events

Administrative change

The following text has been added to replace Section 6.9 which was removed to align the protocol with the new protocol template:

The AstraZeneca representative will be available between visits if the investigator(s) or staff at the center needs information or advice about the study conduct. AstraZeneca medical personnel will be readily available to discuss study related medical questions or problems with the investigator(s). Contact details are provided separately in the Investigator Study File.

Section 6.7 Medication error

This Section has been added to align with the new AstraZeneca Protocol Template.

Section 6.8 Study governance and oversight (Protocol v.2)

The Section has moved to **Section 1.5 Study governance and oversight** to align the protocol with the new AstraZeneca Template.

Section 6.8.2 Non-hematologic toxicity (Table 11, footnote c)

The Section has been amended to clarify that the footnote 'c' applies to venous thromboembolic events.

Section 6.8.3.1 (Table 12)

Table 12 has been amended to provide clarity. Grades have been removed to avoid discrepancy between the Grades earlier used in Table 12 for the description of events for hypertension monitoring and management, and those defined by CTCAE v 4.03.

Section 6.8.3.4 (Table 14)

Table 14 has been simplified by removing text 'on urine dipstick or urinalysis' from the column 'Proteinuria Value if following by urinalysis'.

Section 6.9 Medical emergencies and AstraZeneca contacts (Protocol v.2)

The Section has been placed with the additional text in Section 6.4 ad 9.2 to align with the new AstraZeneca Template. The Sponsor's contact information for medical emergencies will be provided separately to the participating sites in the Investigator Study File, to avoid the need to future amendments due to AZ personnel change.

Section 8.2 Sample size estimate; Section 9.3 Study Timetable and End of Study

The Sections have been amended to clarify the requirement of 20 evaluable patients (ie, with measurable disease [by Investigator assessment]), for interim futility analysis of ORR.

Section 8.5.2 Analysis of the secondary variable(s)

The Section has been revised to clarify for Progression free survival (PFS) and Time to discontinuation of study treatment or death (TDT) summaries as described in the section will also be provided at 18 months.

Section 9.2 Monitoring of the study

Administrative change

Old text

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. The AstraZeneca Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week (see Section 6.9).

New text

The AstraZeneca representative will be available between visits if the Investigator(s) or other staff at the center needs information and advice about the study conduct. **AstraZeneca medical personnel will be readily available to discuss study related medical questions or problems with the investigator(s). Contact details are provided separately in the Investigator Study File.** Rationale for the change The text has been amended to align the protocol with the new AstraZeneca Template. The Sponsor's contact information for medical emergencies will now be provided separately to the participating sites in the Investigator Study File in order to avoid the need for future protocol amendments due to AZ personnel change. **Appendix D Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law.** The Section has been amended to remove all references to Central Labs, as these are not applicable to this study. **Appendix J Acceptable birth control methods**. The Appendix has been amended to make it applicable to both IPs cediranib and olaparib. Cediranib IB recommends that sexually active patients and their partners use two highly effective forms of contraception in combination, throughout the period of taking study treatment and for at least 6 weeks after last dose of study drug(s). This requirement has therefore been changed from 4 weeks (applicable to olaparib), to 6 weeks.

Version 2.0, 27 June 2016 **Changes to the protocol are summarised below:**
Version #2 of the CSP was developed under a previous process where the changes were documented in a separate amendment cover page dated 27 June 2016 and are not listed here.
Version 1.0, 12 May 2016
Initial Creation

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

AstraZeneca

PROTOCOL SYNOPSIS

A single arm, open label, phase IIb study to assess the efficacy and safety of the combination of cediranib and olaparib tablets in women with recurrent platinum resistant epithelial ovarian cancer, including fallopian tube and/or primary peritoneal cancer who do not carry a deleterious or suspected deleterious germline *BRCA* mutation

Principal Investigator

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Study site(s) and number of patients planned

Approximately 60 patients will be enrolled from approximately 40 sites, in the United States.

Study period		Phase of development
Estimated date of first patient enrolled	Q1 2017	IIb
Estimated date of last patient completed	By Q3 2019	IIb

Study design

This is an open label, Phase IIb, single arm, multi-center study to assess the efficacy and safety of the combination of cediranib and olaparib tablets in platinum-resistant relapsed high grade serous, high grade endometroid or clear cell ovarian, fallopian tube or primary peritoneal carcinoma patients who have received at least 3 prior lines of therapy for advanced ovarian cancer and who do not carry deleterious or suspected deleterious germline breast cancer susceptibility gene (*BRCA*) mutations as determined in an appropriately accredited laboratory. Prior antiangiogenic treatment such as bevacizumab, either in a first line or recurrent setting is optional. To be evaluable for the primary endpoint of objective response rate (ORR), all patients should have measurable disease, defined as at least one lesion that can

be accurately measured at baseline by computed tomography (CT) or, if CT is not feasible, magnetic resonance imaging (MRI) and is suitable for repeated assessments per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

Objectives

Primary Objective:	**Outcome Measure:**
To determine the efficacy of the combination of cediranib and olaparib in patients with recurrent platinum resistant epithelial ovarian, fallopian tube and/or primary peritoneal cancer who do not carry deleterious or suspected deleterious germline *BRCA* mutations, as assessed by ORR.	ORR by independent central review (ICR), using RECIST version 1.1.

Secondary Objective:	**Outcome Measure:**
To assess the efficacy of the combination of cediranib and olaparib in this patient population by ORR, duration of response (DoR), disease control rate (DCR), progression free survival (PFS), time to treatment discontinuation or death (TDT) and overall survival (OS).	ORR by Investigator assessment using RECIST 1.1; DoR, PFS and DCR by ICR and Investigator assessment using RECIST 1.1, TDT and OS.
To assess the efficacy of the combination of cediranib and olaparib in patients carrying a somatic deleterious or suspected deleterious variant in either of the *BRCA* genes (*BRCA1* or *BRCA2)* or in homologous recombination repair (HRR)-associated genes identified with current and potential future tumor based *BRCA* or HRR gene mutation assays as assessed by ORR, DoR, DCR, PFS and OS.	ORR, DoR, PFS and DCR by ICR and Investigator assessment using RECIST 1.1, and OS.
To evaluate disease related symptoms and health-related quality of life when compared with baseline data	European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ) C30 and OV-28

Safety Objective:	**Outcome Measure:**
To evaluate the safety and tolerability of the combination of cediranib and olaparib.	Adverse events (AEs), and treatment emergent changes in vital signs and laboratory parameters.

Exploratory Objectives:	**Outcome Measure:**
To assess exploratory biomarkers of potential homologous recombination deficiency (HRD). To assess exploratory angiogenic biomarkers such as vascular endothelial growth factor (VEGF)-A, C, D; sVEGFR2, Tie2, Ang1, 2; leptin; interleukin 6 (IL6) and exploratory immunologic biomarkers. To evaluate exploratory biomarkers of potential resistance/sensitivity to cediranib or olaparib.	Potential biomarker research.
To assess adverse events by patient self-reporting of specific Patient Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE™) symptoms.	Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE™)

Target patient population

Female patients aged ≥18 years, with histologically proven diagnosis of platinum-resistant relapsed high grade serous, high grade endometroid or clear cell ovarian, fallopian tube or primary peritoneal carcinoma who have received at least 3 prior lines of therapy for advanced ovarian cancer, and who do not carry a deleterious or suspected deleterious germline *BRCA* mutation as defined by a local test conducted in an appropriately accredited laboratory (eg, Clinical Laboratory Improvement Amendments [CLIA]-certified) that includes comprehensive DNA sequencing and large rearrangement analysis of *BRCA1* and *BRCA2*. These patients will be required to provide a blood sample prior to receiving investigational products (IPs) which may be used to perform a subsequent confirmatory *BRCA* mutation test using Myriad's BRACAnalysis CDx® test.

Patients who do not know their *gBRCA* status, or whose *gBRCA* status has not been determined by an appropriately accredited laboratory will be required to provide a blood sample at screening to allow determination of *gBRCA* status with Myriad's BRACAnalysis CDx® test. Such patients must fulfill all of the other eligibility criteria, prior to *BRCA* mutation testing being carried out.

All patients should have recurrent platinum-resistant disease, defined as disease recurrence within 6 months (182 days) of the last receipt of platinum-based chemotherapy.

Duration of treatment

There is no maximum duration for taking the study treatments (cediranib + olaparib). Patients should continue on study treatments until:

- Objective radiological disease progression, as defined by RECIST version 1.1 guidelines,
- Unacceptable toxicity,
- Patient withdrawal of consent, or patient meets any other discontinuation criteria.
- Severe non-compliance with the protocol

Both study treatments (cediranib and olaparib) should be discontinued at the same time; patients are not allowed to remain in the study if they are taking either cediranib or olaparib as monotherapy. However, in rare circumstances, patients experiencing ongoing clinical benefit who develop one of the toxicities listed below related to one of the investigational products (IPs) that prevents them to continue to take this IP, may be allowed to continue on the unrelated drug if in the opinion of the treating investigator the risk benefit remains favorable and only after discussion with AstraZeneca Study Physician and the Principal Investigator.

AEs requiring cediranib to be discontinued:

- Gastrointestinal (GI) perforation
- Arterial Thromboembolic Event
- Reversible Posterior Encephalopathy Syndrome (PRES)
- Severe hemorrhage
- Severe persistent hypertension despite maximal anti-hypertensive treatment

AEs requiring olaparib to be discontinued:

- Bone marrow findings consistent with myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML)
- Severe persistent anemia
- Pneumonitis

Once a patient discontinues both cediranib and olaparib, other treatment options are at the discretion of the investigator.

Following discontinuation of study treatment patients will be followed for disease progression by RECIST 1.1 (if they have not already progressed), survival and post-progression anti-cancer therapies until the data cut-off for the primary analysis, approximately 8 months after the last patient has received her first dose of IP. This primary analysis is the final analysis for the study.

Investigational products, dosage and mode of administration

Cediranib

Cediranib is available as a beige film-coated tablet containing 20 mg or 15 mg of cediranib. Patients will be administered cediranib study treatment tablets orally at a dose of 30 mg once daily (od). The planned dose of 30 mg od will be made up of 2 × 15 mg tablets od. One x 20 mg and 1 x 15 mg tablets will be used to manage dose reductions.

Dose reduction steps for cediranib:

Dose Level	Cediranib tablets
Initial dose	30 mg daily
Dose reduction 1	20 mg daily
Dose reduction 2	15 mg daily

Olaparib

Olaparib is available as a green film-coated tablet containing 150 mg or 100 mg of olaparib. Patients will be administered olaparib study treatment tablets orally at a dose of 200 mg twice daily (bd). The planned dose of 200 mg bd will be made up of 2 × 100 mg tablets bd. One x 150 mg and 1 x 100 mg tablets will be used to manage dose reductions.

Dose reduction steps for olaparib:

Dose Level	Olaparib tablets
Initial dose	200 mg twice daily
Dose reduction 1	150 mg twice daily
Dose reduction 2	100 mg twice daily

The dose of cediranib and the morning dose of olaparib can be taken at the same time and can be taken with or without food, in a similar way each morning. The evening dose of olaparib should be taken 12 hours after the morning olaparib dose with or without food in a similar way each day.

Statistical methods

The primary outcome measure is ORR by Independent Central Review (ICR) using RECIST 1.1 criteria. An interim futility analysis of ORR (confirmed and/or unconfirmed complete responses [CR] and partial responses [PR]) will take place after 20 evaluable patients (ie, with measurable disease [by Investigator assessment] at baseline and received at least 1 dose of study drugs) have been followed for at least 4 months. Enrollment will continue whilst the futility analysis is being conducted. The criterion for declaring futility is

based on predictive probability within a Bayesian design framework. If less than 4 of the 20 patients have responded, the study may be stopped for futility. If 4 or more patients have responded the study will continue to the primary analysis.

Assuming the study passes the futility assessment, the data cut-off for the primary analysis of ORR (confirmed CRs + PRs only) will take place 8 months after the last patient has received her first dose of IP, to allow opportunity for all patients to complete at least 4 RECIST follow-up assessments and estimate duration of response (DoR). The primary analysis for the clinical study report (CSR) will be based on the confirmed ORR by ICR using RECIST 1.1 criteria and supported by Investigator assessment of ORR and by other efficacy endpoints (DoR, disease control rate [DCR] and progression free survival [PFS], time to treatment discontinuation or death [TDT]), patient reported outcomes (PROs), and safety and tolerability data. For the primary analysis of ORR by ICR the mean and median of the posterior distribution of ORR will be presented, along with the standard deviation and a 95% credible interval around the mean (based on the highest posterior density [Lee 1997]). ORR by ICR will also be presented with 95% exact (Clopper Pearson) confidence intervals (95% CI).

The posterior probabilities of the ORR being larger than 15%, 20% and 24% will also be computed. To further characterize the response rate, the posterior probability of showing low (<15%), moderate (≥15%- <20%), high (≥20%- <24%) or substantial (≥24%) efficacy will be presented.

At the time of primary analysis, ORR and exact 95% CI (Clopper Pearson) will also be presented for the following:

- ORR by investigator assessment
- ORR for both confirmed and unconfirmed responses for ICR assessment
- ORR in the subgroup of patients carrying a somatic deleterious or suspected deleterious mutation in either of the *BRCA* genes (*BRCA1* or *BRCA2)* or in predefined homologous recombination repair (HRR)-associated genes identified with current and potential future tumor based BRCA or HRR gene mutation assays (ICR and Investigator assessment).

The primary analysis of ORR, and analyses of DoR and DCR by ICR will be produced based on the Evaluable for response (EFR) analysis set; ie, all patients who have received at least one dose of study treatments and have measurable disease at baseline according to the ICR of baseline imaging data. All other efficacy variables (ORR, DoR, DCR based on investigator assessment; PFS, time to treatment discontinuation or death [TDT] and overall survival [OS]), patient reported outcome (PRO) variables and safety variables will be summarized using the Full Analysis set (FAS) comprising all patients who received at least one dose of either of the IPs.

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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
ACE	Angiotensin Converting Enzyme
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase (serum glutamic pyruvate transaminase [SGPT])
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase (serum glutamic oxaloacetic transaminase [SGOT])
AUC	Area under the plasma drug concentration-time curve
BCRP	Breast cancer resistance protein
bd	Twice daily
BP	Blood pressure
BRAT	Bananas, rice, apples, toast
BRCA	Breast cancer susceptibility gene (in accordance with scientific convention, gene and mutation is italicized whereas protein is not italicized)
CA-125	Cancer antigen-125
CI	Confidence interval
CLIA	Clinical Laboratory Improvement Amendments
CR	Complete response
CrCL	Creatinine clearance
CRO	Contract research organization
CSA	Clinical Study Agreement
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
ctDNA	Circulating tumor DNA
CYP	Cytochrome
DAE	Discontinuation of Investigational Product due to Adverse Event

Abbreviation or special term	Explanation
DBP	Diastolic blood pressure
DCR	Disease control rate
DNA	Deoxyribonucleic acid
DoR	Duration of response
DSB	Double-strand break
EC	Ethics Committee, synonymous with Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
(e)CRF	(electronic) Case report form
EFR	Evaluable for response
EOC	Epithelial ovarian cancer
EORTC	European Organization for Research and Treatment of Cancer
ePRO	Electronic patient reported outcome device
FACS	Fluorescence-activated cell sorter
FAS	Full analysis set
FFPE	Formalin fixed, paraffin embedded
FPV	Final Protocol Visit
FT4	Free Thyroxine
gBRCAm	Germline breast cancer susceptibility gene mutated
gBRCAwt	Germline breast cancer susceptibility gene wild type (ie, non-*gBRCAm*)
GCP	Good Clinical Practice
G-CSF	Granulocyte- colony stimulating factor
Geomean	Geometric mean
GGT	Gamma glutamyltransferase
GI	Gastrointestinal
GMP	Good Manufacturing Practice
Hb	Hemoglobin
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRCT	High resolution computed tomography

Abbreviation or special term	Explanation
HRD	Homologous recombination repair deficiency
HRR	Homologous recombination repair
HRQoL	Health-related quality of life
IB	Investigator Brochure
ICH	International Conference on Harmonization
ICR	Independent Central Review
ICU	Intensive care unit
IL6	Interleukin 6
INR	International normalized ratio
IP	Investigational Product
IV	Intravenous
LLN	Lower limit of normal
LSLV	Last Subject Last Visit
LVEF	Left ventricular ejection fraction
MCH	Mean cell hemoglobin
MCV	Mean cell volume
MDS	Myelodysplastic syndrome
MRI	Magnetic resonance imaging
MUGA	Multigated acquisition
N/A	Not available
N/n	Number of subjects
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	Not evaluable
NIH	National Institutes of Health
NTL	Non-target lesion
od	Once daily
ORR	Objective Response Rate
OS	Overall survival
PARP	Polyadenosine 5’diphosphoribose (poly [ADP ribose]) polymerization
PARPi	PARP inhibitor
PBMC	Peripheral blood mononuclear cells

Abbreviation or special term	Explanation
PD	Progressive disease
PFI	Platinum free interval
PFS	Progression free survival
Pgp	P glycoprotein
PI	Principal Investigator
PK	Pharmacokinetics
PLD	PEGylated liposomal doxorubicin
PR	Partial response
PRES	Posterior reversible encephalopathy syndrome
PRO	Patient reported outcome
PRO-CTCAE™	Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events
PSR	Platinum sensitive relapsed
QLQ-C30	Quality of life questionnaire for cancer patients
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RP2D	Recommended Phase II dose
RR	Response rate
RT	Radiotherapy
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Stable disease
SE	Standard error
TDT	Time to treatment discontinuation or death
TSH	Thyroid stimulating hormone
UGT	Uridine diphosphate glucuronosyltransferase
ULN	Upper limit of normal
UPC	Urine protein:creatinine ratio
VEGF	Vascular endothelial growth factor
VEGFR	VEGF receptor
VUS	Variant of unknown significance
WBC	White blood cell count

Abbreviation or special term	Explanation
WBDC	Web Based Data Capture

1. INTRODUCTION

1.1 Background and rationale for conducting this study

1.1.1 Epithelial ovarian cancer

Epithelial ovarian cancer (EOC) is the most lethal gynecologic malignancy and the fifth most common cause of cancer-related death in women with the estimated annual incidence of just over 200,000 individuals and approximately 125,000 deaths (American Cancer Society 2015; Siegel et al 2015).

Most patients with EOC present with advanced disease at diagnosis (Cannistra 2004; Parmar et al 2003). The combination of a platinum drug with a taxane is the standard of care first-line treatment after primary cytoreductive surgery (du Bois et al 2003, McGuire et al 1996). Response to the first-line treatment is achieved in more than 70% of patients whose tumors are optimally or sub-optimally cytoreduced (Ozols et al 2003; Kang et al 2006). However, of those who respond, 55% to 75% will relapse within 2 years of completing treatment (Edwards et al 2015).

A patient's response to first-line platinum-based therapy is indicative of their response to second and subsequent lines of platinum-based treatment, with the length of the platinum-free interval (PFI) and the extent of relapse (site and number of tumors) being particularly prognostic of response. However, most patients will develop resistance to platinum-based therapy over time, with decreasing length of PFI with increasing rounds of treatment. Platinum-resistant ovarian cancer [defined as disease recurring within 6 months (182 days) after the last receipt of platinum based chemotherapy, Stuart et al 2011] has a particularly poor prognosis, with a low response rate (RR) to subsequent chemotherapy (< 15%), median progression free survival (PFS) of 3 to 4 months and overall survival (OS) of approximately 12 months (Davis et al 2014).

Pegylated liposomal doxorubicin (PLD), paclitaxel, topotecan and gemcitabine, the most commonly used agents in the setting of 'platinum resistance' (Luvero et al 2014), show RRs ranging from 10% to 15% and duration of response (DoR) of typically <6 months (Markman et al 2000; Matsuo et al 2010).

Therefore, there is a need to develop alternative therapies for patients with platinum resistant ovarian cancer, given the poor response to traditional cytotoxic agents. Two potential therapeutic targets are DNA damage repair and angiogenesis pathways.

1.1.2 Cediranib

Cediranib is a potent, oral once daily small-molecule tyrosine kinase inhibitor of vascular endothelial growth factor (VEGF)- signalling and angiogenesis that targets all 3 VEGF receptors (VEGFR-1,-2,-3) and has additional activity against stem cell factor receptor (c-kit)-dependent tumor growth.

1.1.2.1 Activity of cediranib as single agent in ovarian cancer patients

Two studies showed the activity of single agent cediranib in recurrent ovarian cancer patients, the National Cancer Institute (NCI)-sponsored studies NCI 7102 (Matulonis et al 2009) and NCI 7129 (Hirte et al 2015); both studies enrolled patients with platinum-sensitive and platinum-resistant disease. Single agent cediranib has shown an objective response rate (ORR) of 17% and a median PFS of 5.2 months in patients with platinum resistant ovarian cancer, treated in 2nd or 3rd line setting (Matulonis et al 2009); another study in platinum resistant ovarian cancer patients treated in 2nd line setting, showed an ORR of 0% (0/35 patients) and a median PFS of 3.7 months (Hirte et al 2015). Results are presented in Table 4.

1.1.2.2 Activity of cediranib in combination with chemotherapy in ovarian cancer patients

The ICON6 study, led by the Medical Research Council, was a Phase III randomized, double-blind, placebo-controlled study in patients with platinum-sensitive relapsed (PSR) ovarian cancer who had received one prior chemotherapy regimen. The ICON6 study recruited 456 women who were randomized 2:3:3 to three parallel treatment arms: in arm A (reference) platinum-based chemotherapy plus placebo; in arm B (concurrent), platinum-based chemotherapy plus cediranib 20 mg, followed by placebo during the maintenance phase; in arm C (concurrent plus maintenance) platinum-based chemotherapy plus cediranib 20 mg followed by single agent cediranib 20 mg during the maintenance phase. Six cycles of chemotherapy were planned, but patients unable to complete 6 cycles and who were responding to treatment could begin maintenance treatment after at least four cycles were completed. Results are summarized in Table 1:

Table 1 ICON6 Summary of Results

Treatment arm	**Arm A (chemotherapy plus placebo followed by placebo in maintenance)** N= 118	**Arm B (concurrent cediranib and chemotherapy followed by placebo in maintenance)** N = 174	**Arm C (concurrent cediranib and chemotherapy followed by maintenance cediranib)** N = 164
Number of progression events (%)	113 (96%)	156 (90%)	141 (86%)
Median PFS in months (95% CI)	8·7 (7·7, 9·4)	9·9 (9·4, 10·5).	11·0 (10·4, 11·7)

Abbreviations: CI confidence interval; N number of subjects; PFS progression free survival

The primary efficacy analysis compared PFS between arm C and arm A; the result showed a hazard ratio (HR) of 0·56, (95% confidence interval [CI]: 0·44–0·72, p<0.0001). The PFS difference between arm B and arm A was also statistically significant (likelihood ratio ptrend<0.0001) demonstrating an effect of maintenance cediranib over and above the effect of

adding it to chemotherapy (Ledermann et al 2016). OS data at 52% maturity showed median OS of 26.3 months in arm C and 21 months in arm A (HR 0.77; 95% CI: 0.55-1.07, p=0.11).

Diarrhea, neutropenia, hypertension, and voice changes were significantly more common, during chemotherapy with cediranib, and diarrhea, hypothyroidism and voice changes were more common during maintenance.

Further details including pre-clinical data and efficacy and safety information are provided in the cediranib (AZD2171) Investigator Brochure (IB).

1.1.3 Olaparib

Olaparib (AZD2281, KU-0059436, Lynparza™) is a potent polyadenosine 5' diphosphoribose [poly (ADP ribose)] polymerization (PARP) inhibitor (PARPi; PARP-1, -2 and -3) which is now approved by FDA as monotherapy in patients with deleterious or suspected deleterious germline breast cancer susceptibility gene (*BRCA*) mutated (as detected by an FDA-approved test) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy.

FDA approval for olaparib was based on data from Study D8180C000042 (Study 42); a Phase II non-comparative study in *gBRCAm* advanced tumors, including ovarian cancer using olaparib capsule formulation, 400 mg bd (Table 2).

Table 2 Overall response and duration of response in patients with *gBRCAm* advanced ovarian cancer who received 3 or more prior lines of chemotherapy

	Olaparib capsule formulation 80 mg bd N = 137
ORR (95% CI)	34 % (26, 42)
Complete response	2%
Partial response	32%
Median DoR in months (95% CI)	7.9 (5.6, 9.6)

Abbreviations: bd twice daily; CI confidence interval; DoR duration of response; *gBRCAm* germline breast cancer susceptibility gene mutation; N number of subjects; ORR objective response rate.

Study 42 data were supported by data from Study D8180C000019 (Study 19); a Phase II, randomized, double-blind, placebo controlled multicenter study using olaparib capsule formulation, 400 mg bd. In Study 19, 265 patients with PSR ovarian cancer in response to platinum based chemotherapy were randomized to olaparib 400 mg bd or placebo in a maintenance setting. The primary analysis demonstrated that maintenance treatment with olaparib led to a significant PFS improvement vs placebo [HR 0.35 [95% CI: 0.25, 0.49]; p<0.00001; Ledermann et al 2012). Moreover, pre-planned subgroup analysis by *BRCA*-mutation status identified patients with *BRCA*-mutated ovarian cancer (n=136, 51.3%)

as the subgroup that derived the greatest clinical benefit from olaparib maintenance monotherapy vs placebo (HR 0.18 [95% CI 0.10, 0.31]; p<0.00001; median 11.2 months versus 4.3 months). A confirmatory study for Study 19, the SOLO2 study is currently ongoing and data are expected to be reported by the end of 2016. SOLO2 is a Phase III randomized, double-blind, placebo controlled multicenter study using olaparib tablet formulation, 300 mg bd. Unlike Study 19, which recruited patients with PSR ovarian cancer, regardless of their *BRCA* mutation status, patients in SOLO2 were required to have a documented *BRCA* mutation.

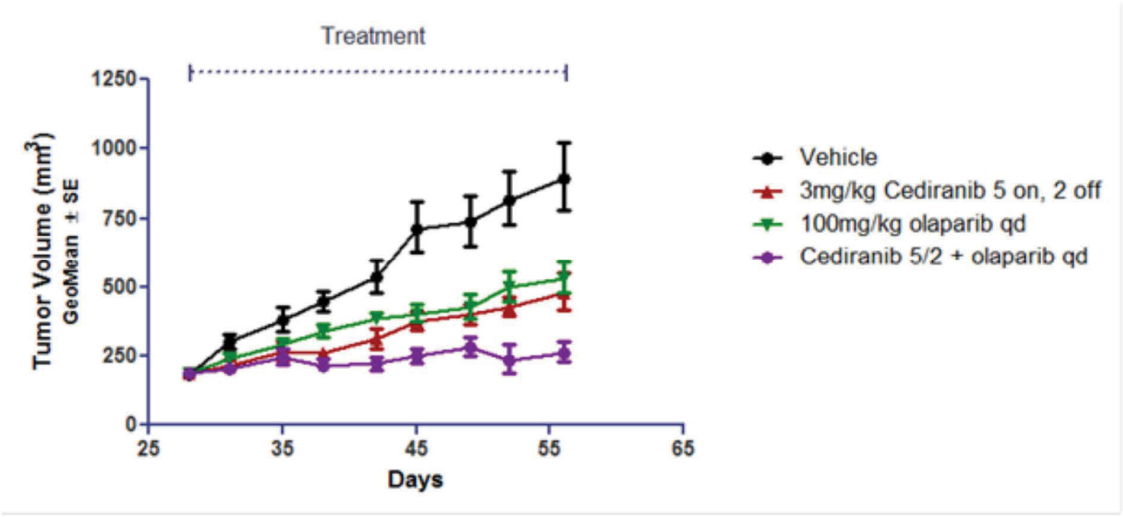
Further details including pre-clinical data and efficacy and safety information are provided in the olaparib (AZD2281) IB.

1.1.4 Activity of the combination of cediranib and olaparib

1.1.4.1 Nonclinical experience with the combination of cediranib and olaparib

To determine whether cediranib has potential to combine with olaparib, the combination treatment was tested in an ovarian patient derived tumor explant model. Tumors were implanted sub-cutaneously, then selected and randomized once they were 0.2 cm^3. Tumor bearing animals were treated with either monotherapy cediranib at 3 mg/kg on a 5 day on 2 day off schedule, olaparib at 100 mg/kg daily, or a combination of cediranib and olaparib. Treatment with both cediranib and olaparib as monotherapies reduced tumor growth, however the combination of the 2 agents resulted in increased anti-tumor activity with tumors not progressing through therapy for the duration of the study.

Figure 1 Combination of cediranib and olaparib in OV2022 patient derived explant.



Tumors were grown to 0.2cm^3 and treated with cediranib once daily (od), olaparib once daily (od) or the combination as indicated. The geometric mean tumor volume is shown +/- Standard error mean
Abbreviations: Geomean geometric mean; od once daily; SE standard error.

Potential mechanism of action for the combination

Specific mechanisms driving the clinical benefit observed with the combination of cediranib and olaparib are currently not defined (Liu et al 2014). However, combining cediranib and olaparib have potential to synergize by increasing the anti-angiogenic effect of cediranib, or preventing the tumor cell from adapting to the anti-angiogenic treatment. Alternatively, cediranib may lower the expression of DNA damage response genes and induce a synthetic "DNA damage response (DDR) phenotype" thereby increasing sensitivity to PARPi.

Cediranib treatment results in a change in vasculature permeability and a reduction in vessels (refer to the cediranib IB for more information). This in turn may induce tumor hypoxia, nutrient and metabolic stress in the tumor cell compartment, specifically, the hypoxia mediated micro-environmental stress has potential to induce both acute DNA damage and suppression of DNA repair pathways with downregulation of homologous recombination genes such as *BRCA1* and *RAD51* and mismatch repair genes (Bindra et al 2005; Bindra et al 2007; Bristow and Hill 2008). This increases the rate of background DNA damage. An increase in metabolic stress as caused by hypoxia would also restrict the potential to generate nucleotides and co-factors to drive DNA repair. Subsequently the combination with olaparib would impair the ability of the tumor cell to tolerate this increase in background DNA damage.

Other mechanisms may also contribute to the combination effect. *BRCA1* can influence the hypoxia response (Kang et al 2006) and hence may prevent cells adapting to the reduction in oxygen. Furthermore, VEGFR3 inhibition can sensitize ovarian cancer cells to chemotherapy via downregulation of BRCA1 and BRCA2 (Lim et al 2014). Other studies have demonstrated that PARP inhibition can result in some anti-angiogenic activity, with PARPi and PARP knockouts showing reduced vascularization in a matrigel plug assay in vivo (Tentori et al 2007).

1.1.4.2 Rationale for treatment with cediranib after prior exposure to bevacizumab

While bevacizumab targets VEGF-A driven activation of VEGFR-1 and -2, evidence is emerging that patients either naturally possess alternative VEGF-VEGFR angiogenesis pathways/features not targeted by bevacizumab and/or acquire reactive resistance to bevacizumab following inhibition of VEGF-A. VEGF-C and/or VEGF-D mediated activation of VEGFR-2 has now emerged as a potential resistance mechanism following inhibition of VEGF-A by bevacizumab (Van der Bilt et al 2012). Recent data show that VEGF-C and its receptor VEGFR-3 are elevated in serum and ascites fluid isolated from ovarian cancer patients. VEGF-C is described as a prognostic marker in ovarian cancer, with patients presenting with high serum VEGF-C (Cheng et al 2013) or high tumor expression (Nishida et al 2004) associated with a worse prognosis. Similar data are described for the related ligand VEGF-D, which also activates VEGFR-3 (Yokoyama et al 2003a; Yokoyama et al 2003b). The selectivity and pharmacokinetic (PK) profile of cediranib, which targets all 3 VEGFRs (VEGFR-1, -2, -3) activated by different ligands (VEGF-A, -B, -C, -D) has the potential to achieve consistent and comprehensive suppression of the VEGF axis for the treatment of ovarian cancer in patients with natural or acquired resistance to bevacizumab.

1.1.4.3 Clinical experience with the combination of cediranib and olaparib

Phase I study cediranib plus olaparib capsules

A Phase I study was initially conducted to establish the recommended Phase II dosing (RP2D) of the cediranib plus olaparib capsule combination, which enrolled a total of 28 patients (20 ovarian, 8 breast). Among the 18 evaluable ovarian patients, an overall ORR of 44% to the cediranib/olaparib combination was observed in this Phase I population, which included both *gBRCAm* patients and patients who did not carry a deleterious or suspected deleterious g*BRCA* mutation (Liu et al 2013). Two dose limiting toxicities (1 Grade 4 neutropenia ≥4 days; 1 Grade 4 thrombocytopenia) occurred at the highest dose level (cediranib 30 mg daily; olaparib 400 mg bd). The RP2D established in this study was cediranib 30 mg od plus olaparib capsules 200 mg bd.

In total, 6 platinum-resistant ovarian cancer patients were treated across all dose levels investigated; the patients comprised of 3 patients who harbored *gBRCAm* mutations (1 patient with each of the following responses: confirmed partial response [PR], unconfirmed PR and stable disease [SD] x 8 months) and 3 patients who did not carry deleterious or suspected deleterious *gBRCA* mutations, or patients whose mutation status was of unknown significance; amongst these patients, 2 had confirmed PRs and 1 patient had SD [<6 months, by CA-125 only]). The ORR was 50%, with a clinical benefit rate of 67%. The median PFS was 7.5 months, with a range of 3.3 to 20.4 months.

Phase I study cediranib plus olaparib tablets

A Phase I study was subsequently conducted to establish the RP2D of cediranib plus olaparib tablets combination; the study enrolled 24 patients with recurrent ovarian, fallopian tube or primary peritoneal cancer. Ten (42%) out of the 24 patients were known to carry a *gBRCA* mutation; 13 patients were non-carriers and 1 patient had unknown *BRCA* status (Liu et al 2013). Among 22 evaluable patients, an overall response rate of 27% was observed. Two of the responders were *BRCA* mutation non-carriers and 4 had platinum resistant disease. The most common toxicities included hypertension, diarrhea and fatigue. The RP2D established for the combination were cediranib 30 mg od plus olaparib tablet 200 mg bd or cediranib 20 mg od plus olaparib tablet 300 mg bd.

Phase II study

A Phase II study comparing the activity of cediranib and olaparib (capsule formulation) combination with olaparib alone in recurrent platinum-sensitive ovarian cancer is ongoing (NCT01116648, Liu et al 2014). In the full analysis set (FAS), there were 2 CRs and 20 PRs in patients who received olaparib monotherapy (48% ORR) and 5 CRs and 30 PRs in patients who received the combination of cediranib and olaparib (80% ORR, p = 0.002). The combination of cediranib and olaparib significantly extended both PFS and ORR compared with olaparib alone, with a median PFS of 9.2 months for olaparib alone and 16.7 months for cediranib/olaparib (HR 0.402, 95% CI 0.217, 0.741, p = 0.0036).

A post-hoc subset analysis of PFS by *BRCA* mutation status (patients with *gBRCAm* vs. patients without *gBRCAm,* including patients with mutation status unknown or variants of

unknown significance [VUS]) showed that in patients who were confirmed to be *gBRCAm*, median PFS was 16.7 months on the olaparib monotherapy arm and 20.2 months on the cediranib/olaparib arm (HR 0.541, 95% CI 0.230, 1.26, p = 0.16). In patients who were not *gBRCAm* or had a VUS, there was a marked increase in PFS from 5.8 months with olaparib monotherapy to 16.6 months with cediranib/olaparib therapy (HR 0.323, 95% CI 0.139, 0.746; p = 0.008) and an increase in ORR from 32% to 76% (p = 0.006). The majority of patients in both arms had received 1 or 2 previous lines of treatment (76% of patients on olaparib monotherapy vs. 82% of patients on cediranib/olaparib arm); it is unclear if the observed difference in ORR and PFS based on *gBRCAm* status could in part be attributable to the degree of prior therapy.

Overall, the cediranib/olaparib combination demonstrated a significant clinical benefit over olaparib alone, as measured both by PFS and ORR. The increased clinical benefit of the cediranib/olaparib combination over olaparib monotherapy was greater in women with tumors that were not *gBRCAm* or who had a VUS status compared with women who harbored *gBRCA1/2* mutations. Toxicities were consistent with expected class-related toxicities of these drugs, with most common grade 3 or 4 toxicities attributed to each of the IPs including fatigue (27% cediranib/olaparib vs. 11% olaparib), diarrhea (23% vs. 0%), and hypertension (41% vs. 0%). There were 2 Common Terminology Criteria for Adverse Event (CTCAE) Grade 4 events, both in the cediranib/olaparib arm: 1 event of Grade 4 hypertension in a patient who was not fully compliant with blood pressure (BP) monitoring and 1 event of Grade 4 myelodysplastic syndrome (MDS).

Summaries of the clinical data in patients with recurrent ovarian cancer for cediranib/olaparib combination compared with single agent olaparib or cediranib are shown in Table 3 and Table 4, respectively.

Table 3 Comparison of cediranib/olaparib and single-agent olaparib in recurrent ovarian cancer trials

Patient characteristics	Treatment	Number of patients	PFS (months)	ORR (%) by RECIST	Reference
gBRCAm (N=47); *gBRCAwt* (N=43) all platinum-sensitive	Olaparib single agent 400 mg bd	46	9.0	56.1	Liu et al 2014
	Cediranib 30 mg od plus olaparib 200 mg bd	44	17.7	83.7	
all *gBRCAm;* all partially platinum sensitive	Olaparib 200 mg bd	32	6.5	25	Kaye et al 2012
	Olaparib 400 mg bd	32	8.8	31	
	PLD 50 mg/m^2	33	7.1	18	
gBRCAm (N=17); non-*gBRCAm* (N=46)	Olaparib 400 mg bd; platinum-sensitive patients	25	N/A	52	Gelmon et al 2011
	Olaparib 400 mg bd; platinum-resistant patients	38	N/A	13	
	Olaparib 400 mg bd; platinum resistant (non-*gBRCAm* only)	26	N/A	4	

Abbreviations: bd twice daily; *gBRCAm* germline *BRCA* mutant; *gBRCAwt* germline *BRCA* wild type; N/A not available; N number of subjects; od once daily; ORR objective response rate; PFS progression free survival; PLD Pegylated liposomal doxorubicin; RECIST Response Evaluation Criteria in Solid Tumors; VUS variant of unknown significance.
Note: these studies used the capsule formulation of olaparib.

Table 4 Comparison of cediranib/olaparib and single-agent cediranib in recurrent ovarian cancer trials

Patient characteristics	Treatment	Number of patients	PFS (months)	ORR (%) by RECIST	Reference
gBRCAm (n=47); *gBRCAwt* (n=43) all platinum-sensitive	Olaparib single agent 400 mg bd	46	9.0	56.1	Liu et al 2014
	Cediranib 30 mg od plus olaparib 200 mg bd	44	17.7	83.7	
N/A	Cediranib 45 mg/30 mg od; overall population	47	5.2	17	Matulonis et al 2009
	Cediranib 30 mg od; platinum-sensitive patients	16	5.2	12.5[a]	
	Cediranib 30 mg od platinum-resistant patients	30	5.2	17[b]	
N/A	Cediranib 45 mg/30 mg od; overall population	74	4.1	N/A	Hirte et al 2015
	Cediranib 45 mg/30 mg od; platinum-sensitive patients	39	7.2	23	
	Cediranib 45 mg/30 mg od platinum-resistant patients	35	3.7	0	

Abbreviations: bd twice daily; *gBRCAm* germline *BRCA* mutant; *gBRCAwt* germline *BRCA* wild type; N/A not available; N number of subjects; od once daily; ORR objective response rate; PFS progression free survival; PLD Pegylated liposomal doxorubicin; RECIST Response Evaluation Criteria in Solid Tumors; VUS variant of unknown significance.

a 6 patients discontinued prematurely for toxicity reasons

b 5 patients discontinued prematurely for toxicity reasons

Note; these studies used the capsule formulation of olaparib.

1.2 Rationale for study design, doses and control groups

Single agent olaparib has shown limited activity in patients with non-*BRCAm* platinum resistant ovarian cancer with ORR 4% (1/26) (Gelmon et al 2011). Single agent cediranib has shown an ORR of 17% and a median PFS of 5.2 months in patients with platinum resistant ovarian cancer, treated in 2nd or 3rd line setting (Matulonis et al 2009); another study in platinum resistant ovarian cancer patients treated in 2nd line setting, showed an ORR of 0% (0/35 patients) and a median PFS of 3.7 months (Hirte et al 2015).

A Phase I trial of the combination of cediranib and olaparib in patients with recurrent ovarian cancer showed that cediranib 30 mg od in combination with olaparib tablet 200 mg bd is a tolerable regimen with preliminary evidence of activity in platinum resistant disease with an ORR of 29% (4/14 patients) including both *BRCA* mutation carriers and non-carriers

(Liu et al 2013). Given the limited activity of single agent olaparib or cediranib in platinum-resistant recurrent ovarian cancer patients who do not carry a deleterious or suspected deleterious *gBRCA* mutation, and the synergistic effect of the combination observed both non-clinically and clinically, it is considered appropriate to evaluate only the combination of olaparib/cediranib using an open-label, single arm design in this patient population of high unmet need for whom there are currently no therapies available other than palliative therapies.

The study thus has the limitation that the current design would not allow an assessment of the contribution components within this study. However, in parallel, a Phase II/III study (NRG-GY005) is investigating in a randomized setting the activity of single agent olaparib and cediranib versus the combination of cediranib plus olaparib and versus standard of care non-platinum based chemotherapy in patients with platinum resistant ovarian cancer who have received no more than 2 prior chemotherapies and may or may not carry *gBRCA* mutation.

Both studies will use the previously established and recommended Phase II dose for the combination of cediranib (30 mg, oral, once daily) plus olaparib tablet 200 mg oral twice daily (Liu et al 2014).

1.3 Benefit/risk and ethical assessment

Ovarian cancer remains a leading cause of death from gynecological cancers in the United States (American Cancer Society 2015) and is the fifth most common cause of cancer mortality in women (Siegel et al 2015). Recurrent platinum resistant high grade serous ovarian cancer accounts for most EOC deaths (Vaughan et al 2011). Effective targeted agents are needed that can improve prognosis with an acceptable toxicity profile without adversely impacting quality of life.

The outlook for patients who develop platinum resistant disease is poor, with a low RR to subsequent chemotherapy (<15%), median PFS of 3 to 4 months and OS of approximately 12 months (Davis et al 2014).

Bevacizumab has recently been approved by the FDA, based on the results of AURELIA trial, in combination with investigator's choice of chemotherapy (paclitaxel, pegylated liposomal doxorubicin [PLD] or topotecan) for the treatment of patients with platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer who received no more than 2 prior chemotherapy regimens. In the 287 patients with responses evaluable by Response Evaluation Criteria in Solid Tumors (RECIST), the ORR was 11.8% versus 27.3% for chemotherapy and bevacizumab plus chemotherapy, respectively (p =0.001; Pujade-Lauraine et al 2014).

Olaparib is approved by the FDA as monotherapy in patients with deleterious or suspected deleterious germline *BRCA* mutated advanced ovarian cancer who have been treated with ≥3 prior lines of chemotherapy and are either platinum sensitive or platinum resistant.

However, patients with platinum resistant ovarian cancer who do not carry a deleterious or suspected deleterious *gBRCA* mutation and who have received ≥3 prior chemotherapy regimens, including prior anti-angiogenic therapy (eg, bevacizumab), do not have effective therapeutic options currently available and there remains a high unmet need for new effective targeted agents for this population. Moreover, efficacy rapidly declines in patients with platinum resistant disease with subsequent lines of therapy and, as per National Comprehensive Cancer network (NCCN) guidelines (NCCN guidelines), palliation should be considered after failure of 2 lines of treatment. Available data demonstrate that the combination of cediranib/olaparib has the potential to provide clinical benefit in this group of patients, with toxicities being consistent with expected class-related toxicities of these drugs (Section 1.1.4.3).

Patients who have progressed on prior anti-angiogenic therapy (eg, bevacizumab) have been reported to have an increase in alternate VEGF ligands suggesting that a more comprehensive inhibition of VEGF signaling as offered by cediranib may be appropriate at that point (Lieu et al 2013). Therefore, there remains an unmet medical need for effective treatment options with an alternative anti-angiogenic treatment for patients at their relapse on bevacizumab.

On balance, therefore the benefit/risk for the combination of cediranib plus olaparib in heavily pre-treated patients with platinum-resistant recurrent ovarian cancer patients who do not carry a deleterious or suspected deleterious *gBRCA* mutation, for whom only palliative therapies are available, is considered favorable.

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonization (ICH) Good Clinical Practice (GCP), applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

1.4 Study Design

This is an open label, Phase IIb, single arm, multi-center study to assess the efficacy and safety of the combination of cediranib and olaparib in platinum resistant relapsed high grade serous, high grade endometroid or clear cell ovarian, fallopian tube or primary peritoneal carcinoma who have received at least 3 prior lines of therapy for advanced ovarian cancer and who have no evidence of deleterious or suspected deleterious *gBRCA* mutation(s) as defined by a local test conducted in an appropriately accredited laboratory (eg, Clinical Laboratory Improvement Amendments [CLIA]-certified) that includes comprehensive DNA sequencing and large rearrangement analysis of *BRCA1* and *BRCA2*. Prior antiangiogenic treatment such as bevacizumab, either in a first line or a recurrent setting is optional. To be eligible to enter the study, all patients should have measurable disease (as assessed by the Investigator), defined as at least 1 lesion that can be accurately assessed at baseline by computed tomography (CT)/ magnetic resonance imaging (MRI) and is suitable for repeated assessment per RECIST 1.1. All patients will have RECIST 1.1 tumour assessments at screening (within 28 days prior to the start of study treatment) and every 8 weeks (±1 week) after start of treatment until objective radiological disease progression or withdrawal of consent. Objective radiological response on treatment (complete response [CR] or PR) will need to be confirmed

during next RECIST 1.1 visit assessment to ensure that identified responses are not a result of measurement error in a single arm clinical trial.

Patients will receive the combination of:

- Cediranib tablets 30 mg oral once daily
- Olaparib tablets 200 mg oral twice daily

Patients should continue to receive IPs until objective radiological disease progression, unacceptable toxicity or withdrawal of consent. The study originally planned to recruit 100 patients over approximately 12 months. Due to slower than projected recruitment, the study now plans to recruit approximately 60 patients. An interim futility analysis will be undertaken once the first 20 evaluable patients (ie, with measurable disease [by Investigator assessment] and have received at least 1 dose of IP) have been followed for at least 4 months. If fewer than 4 radiological tumor responses are observed at this point, the trial may be considered futile and enrollment stopped. Enrollment will continue whilst the futility analysis is being conducted.

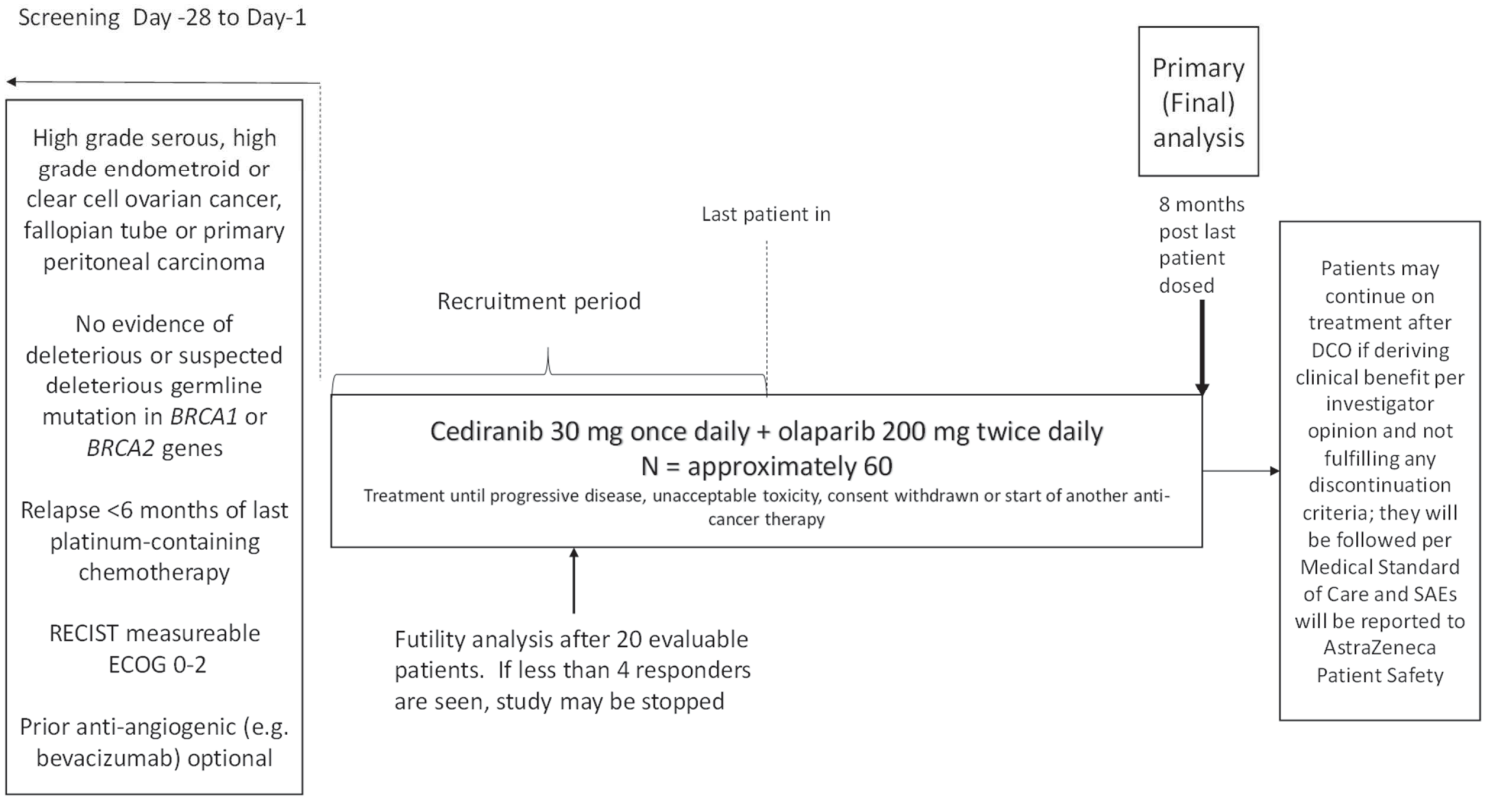
The primary analysis of the study will be based on measurement of ORR in the evaluable for response (EFR) analysis set (CR+PR; confirmed responses only) by Independent Central review (ICR) using RECIST 1.1. The primary analysis will also report analyses of DoR and disease control rate (DCR) by ICR in the EFR analysis set. Other variables analyzed at the primary analysis (ORR, DoR, DCR based on investigator assessment; PFS, overall survival [OS], time to treatment discontinuation or death [TDT], patient-reported outcome [PRO] variables and safety variables) will be summarized using the FAS. The data cut-off for the primary analysis will take place 8 months after the last patient has received her first dose of IP and is the final analysis for the study. This primary data cut-off will be followed by clinical database lock.

Patients continuing to receive clinical benefit without meeting any discontinuation criteria during the study, will complete a FPV which will occur at their last scheduled visit prior to the primary data cut-off. Beyond the FPV, patients may continue to receive cediranib and/or olaparib if they are deriving clinical benefit in the opinion of the investigator, and not fulfilling any discontinuation criteria (see Section 4.5).

All patients will be required to provide an archival formalin fixed, paraffin embedded (FFPE) tumor sample from the primary or preferably recurrent cancer. If an archival tumor sample is not available, a tumor sample from a fresh biopsy is acceptable. Please note that a lesion that has been biopsied during screening cannot be selected as a target lesion for RECIST assessment. Tumor samples will be tested for somatic (ie, non-germline) deleterious or suspected deleterious mutation in either of the *BRCA* genes (*BRCA1* or *BRCA2*) and the following homologous recombination repair (HRR)-associated genes: *ATM, BRIP1, PALB2, RAD51C, BARD1, CDK12, CHEK1, CHEK2, FANCL, PPP2R2A, RAD51B, RAD51D,* and *RAD54L*.

The design of the study is shown in Figure 2:

Figure 2 Study flow chart



Abbreviations: *BRCA* breast cancer susceptibility gene; DCO data cut-off; ECOG Eastern Cooperative Oncology Group; N number of subjects; RECIST Response Evaluation Criteria in Solid Tumors; SAE serious adverse event.

1.5 Study governance and oversight

The patient safety data from the study will be closely monitored on an ongoing basis by the Sponsor and a Study Steering Committee. Issues identified will be addressed; for instance, this could involve amendments to the study protocol and letters to Investigators.

1.5.1 Steering Committee

The Steering Committee will consist of two investigators (including the Principal Investigator) and AZ representatives including clinician, statistician and clinical scientist. The remit is to review the outcomes of the planned analyses conducted during the conduct of the trial including the futility analysis and the primary analysis. In addition, safety topics can be reviewed as needed. The steering committee's remit is to provide an agreed strategic direction for the study.

1.5.2 Data Monitoring Committee

In this Phase IIb study, a Data Monitoring Committee was not considered necessary as it is an open label study and the safety profiles of olaparib and cediranib as monotherapies and in combination, have previously been established.

2. STUDY OBJECTIVES

2.1 Primary objective

Primary Objective:	Outcome Measure:
To determine the efficacy of the combination of cediranib and olaparib in patients with recurrent platinum resistant epithelial ovarian, fallopian tube and/or primary peritoneal cancer who do not carry deleterious or suspected deleterious germline *BRCA* mutations, as assessed by objective response rate (ORR).	ORR by independent central review (ICR) using RECIST version 1.1

2.2 Secondary objectives

Secondary Objective:	Outcome Measure:
To assess the efficacy of the combination of cediranib and olaparib in this patient population by ORR, duration of response (DoR), disease control rate (DCR), progression free survival (PFS), time to treatment discontinuation or death (TDT) and overall survival (OS).	ORR by Investigator assessment using RECIST 1.1; DoR, PFS and DCR by ICR and Investigator assessment using RECIST 1.1, TDT and OS.
To assess the efficacy of the combination of cediranib and olaparib in patients carrying a somatic deleterious or suspected deleterious variant in either of the *BRCA* genes (*BRCA1* or *BRCA2)* or in HRR-associated genes identified with current and potential future tumor based *BRCA* or HRR gene mutation assays as assessed by ORR, DoR, DCR, PFS and OS	ORR, DoR, PFS and DCR by ICR and Investigator assessment using RECIST 1.1, and OS
To evaluate disease related symptoms and health-related quality of life when compared with baseline data	European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ) C30 and OV-28

2.3 Safety objectives

Safety Objective:	Outcome Measure:
To evaluate the safety and tolerability of the combination of cediranib and olaparib	Adverse events (AEs), and treatment emergent changes in vital signs and laboratory parameters.

2.4 Exploratory objectives

Exploratory Objectives:	Outcome Measure:
To assess exploratory biomarkers of potential homologous recombination repair deficiency (HRD). To assess exploratory angiogenic biomarkers such as vascular endothelial growth factor (VEGF)-A, C, D; sVEGFR2, Tie2, Ang1, 2; leptin; interleukin 6 (IL6) and exploratory immunologic biomarkers. To evaluate exploratory biomarkers of potential resistance/sensitivity to cediranib or olaparib.	Potential biomarker research
To assess adverse events by patient self-reporting of specific Patient Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE™) symptoms.	Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE™)

3. PATIENT SELECTION, ENROLLMENT, RANDOMIZATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

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

Patients who have prior documented evidence that they do not carry deleterious or suspected deleterious *gBRCA* mutation(s), as defined by a local test conducted in an appropriately accredited laboratory (eg, CLIA-certified) that includes comprehensive DNA sequencing and large rearrangement analysis of *BRCA1* and *BRCA2,* may be enrolled provided they fulfill all of the inclusion criteria and none of the exclusion criteria. These patients will be required to provide a blood sample prior to receiving investigational products (IPs) which may be used to perform a subsequent confirmatory *BRCA* mutation test using Myriad's BRACAnalysis CDx® test.

Patients who do not know their *gBRCA* status, or whose *gBRCA* status has not been determined by an appropriately accredited laboratory will be required to provide a blood sample at screening to allow determination of *gBRCA* status with Myriad's BRACAnalysis CDx® test. Such patients must fulfill all of the other eligibility criteria, prior to *BRCA* mutation testing being carried out.

3.1 Inclusion criteria

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

1. Ability and willingness to provide written informed consent, and to comply with the requirements of the protocol.

2. Females aged ≥18 years with previous histologically proven diagnosis of high grade serous, high grade endometroid or clear cell ovarian cancer, fallopian tube or primary peritoneal carcinoma.

3. No evidence of deleterious or suspected deleterious germline mutation in *BRCA1* or *BRCA2* genes. *BRCA1* and/or *BRCA2* variants that are classified as "Variants of uncertain clinical significance" or "Variant of unknown significance (VUS)" are eligible, as well as "Variant, favor polymorphism" or "benign polymorphism".

4. Recurrent platinum-resistant disease, defined as disease progression within 6 months (182 days) of the last receipt of platinum-based chemotherapy.

    - Patients with platinum refractory disease defined as disease progression during the last receipt of platinum-based therapy are not eligible.

    - Patients with primary platinum resistant/refractory disease defined as progression during or within 6 months (182 days) of completing first-line platinum based chemotherapy are not eligible.

5. CT/MRI evidence of measurable disease as per RECIST 1.1 defined as at least one lesion, not previously irradiated, that can be accurately measured at baseline as ≥ 10 mm in the longest diameter (except lymph nodes which must have short axis ≥ 15 mm) and which is suitable for accurate repeated measurements

6. Eastern Cooperative Oncology Group (ECOG) performance status 0-2; see Appendix E

7. Life expectancy ≥12 weeks

8. Prior receipt of antiangiogenic treatment, including but not limited to bevacizumab, is optional. If used, it can be in the first line or recurrent setting.

9. At least 3 prior lines of therapy for advanced ovarian cancer as follows:

    – Platinum chemotherapy: at least two prior lines required

    – Non-platinum chemotherapy: up to two prior lines are allowed but not required.

- Hormonal therapy (such as tamoxifen, aromatase inhibitors), bevacizumab (or other angiogenesis inhibitor), or other immunotherapy used as a single agent will not count as a line of chemotherapy.

10. Confirmation of the availability of a formalin fixed, paraffin embedded (FFPE) tumor sample (or approximately unstained 20 sections mounted on glass slides prepared from the block) from the primary or recurrent cancer must be provided. All attempts should be made to provide the sample prior to first dose or soon thereafter. If archival tumor sample is not available, tumor sample from fresh biopsy is acceptable; however, any lesion biopsied during screening can no longer be selected as a target lesion.

11. Patients must have adequate organ and marrow function measured within 28 days prior to administration of IPs as defined below:

- Hemoglobin (Hb) ≥10.0 g/dL with no blood transfusion in the past 28 days
- Absolute neutrophil count (ANC) ≥1.5 x 10^9/L
- Platelet count ≥100 x 10^9/L
- Total bilirubin ≤1.5 x institutional upper limit of normal (ULN)
- Aspartate aminotransferase (AST) (Serum Glutamic Oxaloacetic Transaminase [SGOT]) / Alanine aminotransferase (ALT) (Serum Glutamic Pyruvate Transaminase [SGPT])]) ≤3 x institutional upper limit of normal (ULN)
- Creatinine clearance ≥50 mL/min
- Urine protein:creatinine ratio (UPC) ≤1 OR proteinuria ≤2+ on two consecutive dipsticks taken no less than 1 week apart. Patients with 2+ proteinuria on dipstick must also have UPC <0.5 on 2 consecutive samples.

12. Adequately controlled blood pressure (systolic blood pressure [SBP] ≤140 mmHg; diastolic blood pressure [DBP] ≤ 90mmHg) on maximum of 3 antihypertensive medications. Patients must have a blood pressure (BP) of ≤ 140/90 mmHg taken in the clinic setting by a medical professional within 2 weeks prior to starting study. It is strongly recommended that patients who are on three antihypertensive medications be followed by a cardiologist or a primary care physician for management of BP while on study. Patients must be willing and able to check and record daily blood pressure readings.

13. Adequately controlled thyroid function, with no symptoms of thyroid dysfunction

14. Able to swallow and retain oral medications and without gastrointestinal (GI) illnesses that would preclude absorption of cediranib or olaparib.

15. Postmenopausal or evidence of non-childbearing status for women of childbearing potential as confirmed by a negative urine or serum pregnancy test within 7 days prior to start of IPs. Postmenopausal is defined as:

- Age ≥60 years, or
- Age <60 with any one or more of the conditions below:
  - Amenorrheic for ≥1 year in the absence of chemotherapy and/or hormonal treatments,
  - Luteinizing hormone and/or Follicle stimulating hormone and/or estradiol levels in the post-menopausal range,
  - Radiation-induced oophorectomy with last menses >1 year ago,
  - Chemotherapy-induced menopause with >1 year interval since last menses,
  - Surgical sterilization (bilateral oophorectomy or hysterectomy).

3.2 Exclusion criteria

Patients must 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 both AstraZeneca staff and/or staff at the study site)
2. Previous enrollment in the present study
3. Exposure to any IP during the last 4 weeks prior to enrollment.
4. Previous treatment with PARP inhibitor. For this study, BSI-201 (iniparib) is not considered as PARPi.
5. Recent cancer-directed therapies: Radiotherapy (RT) within 4 weeks, chemotherapy or other systemic anti-cancer therapy within 4 weeks, hormonal therapy within 2 weeks, or prior anti-angiogenic treatment (eg, bevacizumab) within 6 weeks prior to starting treatment.
6. Cancer antigen-125 (CA-125) only disease without RECIST 1.1 measurable disease.
7. Major surgical procedure within 2 weeks prior to starting treatment; patients must have recovered from any effects of any major surgery and surgical wound should have healed prior to starting treatment.

8. Clinically significant signs and/or symptoms of bowel obstruction within 3 months prior to starting treatment.

9. History of intra-abdominal abscess within 3 months prior to starting treatment.

10. History of GI perforation. Patients with a history of abdominal fistula will be considered eligible if the fistula was surgically repaired, there has been no evidence of fistula for at least 6 months prior to starting treatment, and patient is deemed to be at low risk of recurrent fistula.

11. Other malignancy within the last 5 years except for:

- Curatively treated basal cell or squamous cell carcinoma of skin; in situ cancer of the cervix, ductal carcinoma in situ of the breast or stage 1, grade 1 endometrial carcinoma.

- Curatively treated other solid tumors including lymphomas (without bone marrow involvement) with no evidence of disease for ≥5 years prior to start of IPs.

12. Persisting ≥Grade 2 CTCAE toxicity (except alopecia and Grade 2 peripheral neuropathy) from previous anti-cancer treatment(s).

13. Central nervous system metastases:

- Symptomatic uncontrolled brain metastases requiring corticosteroid treatment. History of spinal cord compression unless after definitive treatment the patient has clinically stable disease (SD) for at least 28 days prior to starting IPs. In the absence of these features and in an asymptomatic patient a scan to confirm the absence of brain metastases is not required.

14. Patients with any of the following:

- History of myocardial infarction within 6 months prior to starting treatment

- Unstable angina

- Resting electrocardiogram (ECG) with clinically significant abnormal findings

- New York Heart Association functional classification of III or IV.

15. Left ventricular ejection fraction (LVEF) < lower limit of normal (LLN) per institutional guidelines, or <55%, if threshold for normal not otherwise specified by institutional guidelines, for patients with the following risk factors:

- Prior treatment with anthracyclines

- Prior treatment with trastuzumab
- Prior central thoracic RT, including exposure of heart to therapeutic doses of ionizing RT
- History of myocardial infarction within 6-12 months prior to start of IPs
- Prior history of other significant impaired cardiac function

16. History of stroke or transient ischemic attack within 6 months

17. Uncontrolled intercurrent illness including, but not limited to known ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, extensive interstitial bilateral lung disease on High Resolution Computed Tomography (HRCT) scan or psychiatric illness/social situations that would limit compliance with study requirements.

18. Patients with myelodysplastic syndrome (MDS)/treatment-related acute myeloid leukemia (t-AML) or with features suggestive of MDS/AML

19. No prior allogeneic bone marrow transplant or double umbilical cord blood transplantation.

20. Known active human immunodeficiency virus (HIV), Hepatitis B or Hepatitis C infection on antiviral treatment.

21. Concomitant use of known strong cytochrome (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 treatments is 2 weeks for strong inhibitors, and at least 1 week for moderate inhibitors.

22. Concomitant use of known strong CYP3A inducers (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 treatments is 5 weeks for enzalutamide or phenobarbital and 4 weeks for other agents.

For procedures for withdrawal of incorrectly enrolled patients see Section 3.4.

3.3 Patient enrollment and randomization

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

The Investigator(s) will:

1. Obtain signed informed consent from the potential patient or their guardian/legal representative before any study specific procedures are performed.

2. Assign potential patient a unique enrollment number, beginning with 'E#' through the Interactive Response Technology system. This number is the patient's unique identifier and is used to identify the patient on the electronic case report forms (eCRFs).

3. Determine patient eligibility. See Section 3.

If a patient withdraws from participation in the study, then her enrollment code cannot be reused.

This is an open-label study; there is no randomization.

3.4 Procedures for handling incorrectly enrolled patients

3.4.1 Screen failures

Screening failures are patients who do not fulfil the eligibility criteria for the study, and therefore must not be entered into the study. Patients who fail to meet the eligibility criteria should not, under any circumstances, enter the study or receive IPs. There can be no exceptions to this rule.

3.4.2 Incorrectly enrolled patients

Where a patient does not meet all the eligibility criteria but is enrolled 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 continue or discontinue the patient from treatment. The AstraZeneca study physician must ensure all decisions are appropriately documented.

3.5 Methods for assigning treatment groups

Not applicable; this is a single arm study.

3.6 Methods for ensuring blinding

Not applicable; this is an open-label, unblinded, study.

3.7 Methods for unblinding

Not applicable; this is an open-label, unblinded, study.

3.8 Restrictions

Patients should not donate blood while participating in this study and for at least 3 months following the last dose of IPs.

Absorption of oral contraceptives can be impaired in case of GI symptoms such as diarrhea >24 hours or vomiting. In addition, the possibility that cediranib may induce GI CYP3A and uridine diphosphate glucuronosyltransferase (UGT) enzymes cannot be excluded and the efficacy of hormonal contraceptives may be reduced if co administered with cediranib.

Therefore, women of child-bearing potential must agree to use two highly effective forms of contraception (see Appendix J) during study treatment and for at least 6 weeks after discontinuation of study treatment and to perform pregnancy tests as required (see Sections 5.2.5.1, 6.6.1). Should a woman become pregnant or suspect she is pregnant during the study conduct, she should inform her treating physician immediately. Breast-feeding is contraindicated whilst receiving IPs.
Restrictions related to pregnancy are provided in Section 6.6. Restrictions related to concomitant medications (including medications metabolized via CYP3A4/5 or P glycoprotein (PgP)/UGT; anticoagulant therapy; anti-emetics/anti-diarrheal therapies; palliative RT and administration of other anti-cancer agents) are described in Section 7.7 and Appendix I.

Patients may not use any complementary or alternative medicines including natural herbal products or folk remedies as they may interfere with the effectiveness of the IPs.

It is prohibited to consume grapefruit juice while on olaparib therapy.

3.9 Discontinuation of investigational product

Patients may be discontinued from IPs in the following situations:

- Patient decision; the patient is at any time free to discontinue treatment, without prejudice to further treatment. A patient who discontinues treatment is normally expected to continue to participate in the study unless she specifically withdraws her consent to further participation in any study procedures and assessments (see Section 3.10.1).
- Adverse Event (AE), including AEs that meet criteria for discontinuation as defined in Section 6.7; any AEs that, in the opinion of the Investigator or AstraZeneca, contraindicates further dosing.
- Objective progression according to RECIST version 1.1 criteria.
- Severe non-compliance with the protocol

Both IPs (cediranib and olaparib) should be discontinued at the same time; patients are not allowed to remain in the study if they are taking either cediranib or olaparib as monotherapy.

However, in rare circumstances, patients experiencing ongoing clinical benefit but who develop one of the toxicities listed below, related to one of the IPs, that prevents them to continue to take this IP, may be allowed to continue on the unrelated drug if in the opinion of the treating investigator the risk benefit remains favorable and only after discussion with the AstraZeneca Study Physician and the Principal Investigator.

AEs requiring cediranib to be discontinued:

- GI perforation
- Arterial Thromboembolic Event
- Reversible Posterior Encephalopathy Syndrome (PRES)
- Severe hemorrhage
- Severe persistent hypertension despite maximal anti-hypertensive treatment

AEs requiring olaparib to be discontinued:

- Bone marrow findings consistent with MDS/AML.
- Severe persistent anemia
- Pneumonitis

Refer to Section 6.7 for more information on the management of IP-related toxicities.

3.9.1 Procedures for discontinuation of a patient from investigational product

At any time, patients are free to discontinue IPs (ie, both cediranib and olaparib treatments) or withdraw from the study (ie, both cediranib and olaparib treatments and assessments) without prejudice to further treatment. If a patient is withdrawn from study, see Section 3.10.

A patient that decides to discontinue the IPs 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). AEs will be followed up (see Section 6) and all study drugs should be returned by the patient.

By discontinuing from IPs, the patient is not withdrawing from the study. Any patient discontinuing the IPs should attend the scheduled Treatment Discontinuation visit, and the Follow Up visit 30 days post-discontinuation for the assessments outlined in the study schedule. After discontinuation of IPs, 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 eCRF the date and reasons of discontinuation, any clinical manifestations and treatments required at the time of discontinuation.

Any patient who has not yet shown objective radiological disease progression at discontinuation from cediranib and olaparib treatments should continue to be followed as per RECIST as detailed in Section 4 (ie, patients should be followed for progression by tumor assessments every 8 weeks). Following objective radiological progression, patients should also be followed for survival as detailed in Section 5.1.4.

After discontinuation of the IPs at any point in the study, all ongoing AEs or serious adverse events (SAEs) must be followed until resolution unless, in the Investigator's opinion the condition is unlikely to resolve due to the patients underlying disease, or the patient is lost to follow up (see Section 6.3.2) or until the patient starts new anti-cancer treatment. All new AEs and SAEs occurring during the 30 calendar days after the last dose of IPs must be reported (if SAEs, they must be reported to AstraZeneca within 24 hours as described in Section 6.4) and followed to resolution as above. For guidance on reporting AEs after the 30 day follow up period see Section 6.3.3.

All patients must be followed for survival, up to the data cut-off for the primary analysis. If a patient is withdrawn from study, see Section 3.10.

3.10 Criteria for withdrawal

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 ie, the patient does not meet the required inclusion/exclusion criteria for the study (please refer to Section 3.4).
- Patient lost to follow-up.
- Death.

*If a patient withdraws consent, they will be specifically asked if they are withdrawing consent to continue further treatment with study medication:

- BUT are willing to remain in the study and have further follow up (eg, CT/MRI assessments, survival calls)
- OR are also withdrawing consent to follow up; thereby withdrawing consent to participate in the study

- AND if they are withdrawing consent for the use of any samples (tumor or blood) Data obtained prior to withdrawal of consent will be maintained in the clinical database and used in the study reporting (see Section 5.7.6).

3.10.1 Withdrawal of the informed consent

Patients are free to withdraw from the study at any time (IPs 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 her enrollment code cannot be reused. Withdrawn patients will not be replaced.

If the patient is lost to follow-up, the Investigator should make every reasonable effort to contact the patient or a responsible relative. Patients will be considered lost to follow-up only if no contact has been established at any time up to data cut-off for the primary analysis, such that there is insufficient information to determine the patient's status at that time. Patients who refuse to continue participation in the study, including telephone contact, should be documented as "withdrawal of consent" rather than "lost to follow-up." Investigators should document attempts to re-establish contact with missing patients throughout the study period. If contact with a missing patient is re-established, the patient should not be considered lost to follow-up and any evaluations should resume according to the protocol.

3.10.2 Survival status for withdrawn consent and lost to follow up patients

At the time of primary analysis, the survival status of all patients in the full analysis set should be re-checked, this includes those patients who withdrew consent or are classified as "lost to follow up."

- Lost to Follow up – site personnel should check hospital records, the patients' current physician, and a publicly available death registry (if available) to obtain a current survival status in the 2 weeks following data cut-off. (The SURVIVE module will be updated.)
- In the event that the patient has actively withdrawn consent to the processing of their personal data, the survival status of the patient can be obtained by site personnel from publicly available death registries or resources (if available) where it is possible to do so under applicable local laws to obtain a current survival status in the 2 weeks following data cut-off. (The SURVIVE module will be updated.)

3.11 Discontinuation of the study

The study may be stopped if, in the judgement of AstraZeneca, trial patients are placed at undue risk because of clinically significant findings that are not considered to be consistent with continuation of the study, or if the futility boundary is met at the Interim Analysis.

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 eCRF. 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

Table 5 shows the Schedule of Study Assessments.

Table 5 Schedule of study assessments

	Screening	Treatment Period					Study treatments discontinued	Follow-up period			FPV[a]	For details, see protocol section
Week			**Day 1 to Week 4**	**Week 4 to Week 8**	**Week 8 onwards**			**N/A**	**N/A**	**N/A**		
Visit (window)	**Day -28 to -1**	**Study Day 1**	**Weekly (±3 days)**	**Every 2 weeks (±3 days)**	**Every 4 weeks (±3 days)**	**Every 8 weeks (±1 week)**		**Day 30 Follow-up (±3 days)**	**Follow-up for progression[b]**	**Survival Follow-up**		
Informed consent	X											3.3
Determine Eligibility[c]	X											3.1/3.2
Demographics, height	X											4.1/5.2.2
Medical history[d]	X											4.1
Germline *BRCA* status[e]	X											5.7.1
Archival tumor tissue sample	X											5.7.2
Adverse Events[f]	X	←	—	—	—	—	—	→			X	6
Concomitant medication[g]	X		←	—	—	—	—	—	—	→	X	7.7
Physical Examination	X	X[h]			X		X	X			X	4.1/5.2.2
Performance Status (ECOG)	X										X	4.1
Vital signs[i], weight[j]	X	X	X	X	X		X	X			X	5.2.2/5.2.4
ECG[k]	X										X	5.2.3

Table 5 Schedule of study assessments

	Screening	Treatment Period					Study treatments discontinued	Follow-up period			FPV[a]	For details, see protocol section
Week			**Day 1 to Week 4**	**Week 4 to Week 8**	**Week 8 onwards**			**N/A**	**N/A**	**N/A**		
Visit (window)	**Day -28 to -1**	**Study Day 1**	**Weekly (±3 days)**	**Every 2 weeks (±3 days)**	**Every 4 weeks (±3 days)**	**Every 8 weeks (±1 week)**		**Day 30 Follow-up (±3 days)**	**Follow-up for progression[b]**	**Survival Follow-up**		
Pregnancy Test[l] For women of childbearing Potential	X[l]	X	X	X	X						X	5.2.5.1
LVEF[m]	X											6.8.3.6
Urinalysis[n]	X	X			X		X	X				5.2.1.4
Hematology[o,p]	X	X	X	X	X		X	X			X	5.2.1.1
Biochemistry[o q]	X	X	X	X	X		X	X			X	5.2.1.2
CA-125	X	Every 8 weeks relative to first dose until disease progression										5.2.1.3
TSH, FT4	X					X					X	5.2.1.2
Tumor assessments by CT/MRI scan[r]	X	Every 8 weeks relative to first dose until disease progression										5.1.1
Biomarker plasma and blood PBMC samples[s]	X		Week 4	Week 8			X[r]					5.7.2
Blood biomarker sample for ctDNA	X						X					5.7.2

Table 5 Schedule of study assessments

	Screening	Treatment Period					Study treatments discontinued	Follow-up period			FPV[a]	For details, see protocol section
Week			**Day 1 to Week 4**	**Week 4 to Week 8**	**Week 8 onwards**			**N/A**	**N/A**	**N/A**		
Visit (window)	**Day -28 to -1**	**Study Day 1**	**Weekly (±3 days)**	**Every 2 weeks (±3 days)**	**Every 4 weeks (±3 days)**	**Every 8 weeks (±1 week)**		**Day 30 Follow-up (±3 days)**	**Follow-up for progression[b]**	**Survival Follow-up**		
EORTC-QLQ-C30/ EORTC-QLQ-OV28 (by electronic device)		X	Every 8 weeks relative to first dose until discontinuation of IPs				X	X				5.3.1.1
PRO-CTCAE (by electronic device)		X	Weekly for the first 12 weeks, then every 4 weeks (relative to first dose) until discontinuation of IPs					X				5.3.1.2
PK Sample (plasma)[t]			Week 4 only	Week 8 only								5.4.1
Survival and subsequent anticancer therapies[u]							Every 8 weeks from discontinuation or progression					5.1.4
Compliance with investigational products[v]		X	X	X	X		X					7.5

a. The FPV applies to patients continuing to receive clinical benefit without meeting any discontinuation criteria during the study and will occur at their last scheduled visit prior to data cut-off. Beyond FPV, patients may continue to receive cediranib and/or olaparib if they are deriving clinical benefit in the opinion of the investigator, and not fulfilling any discontinuation criteria. Such patients are to be followed in accordance with the Medical Standard of Care and as deemed appropriate by the investigators. SAE reporting (on paper) will continue to ensure safety data collection and monitoring of the patients while receiving the investigational product. Patients will continue to be monitored for all SAEs and pregnancies while receiving IPs and for 30 days after the last dose of IPs.
b. Progression follow-up only required for patients who discontinue IPs prior to disease progression
c. Review inclusion and exclusion criteria and ensure eligibility prior to enrolment
d. Obtain relevant medical history, including all treatments for ovarian cancer in the past and any unresolved toxicity.
e. All patients whose *gBRCA* status is unknown or not determined by a local test conducted in an appropriately accredited laboratory, a blood sample for prospective analysis of g*BRCA* mutation status is required during screening. Patients who do not carry deleterious or suspected deleterious germline *BRCA* mutation as determined

by a local test conducted in an appropriately accredited laboratory, may be enrolled on the basis of a documented test result; however, a blood sample is required prior to first dose of study treatments, which may be used for confirmation of the result in a retrospective analysis.

f. Patients should be closely monitored for adverse events which should be recorded, as they occur. SAEs that occurred during screening period will also be recorded. Patient diary data (via handheld electronic device) for blood pressure and diarrhea will be reviewed by the Investigator at each patient visit and any AEs and/or SAEs recorded in the AE eCRF

g. All concomitant treatments will be recorded while the subject is taking IPs, together with the indication for which they are used

h. Repeat assessment not required on Day 1, if already performed during previous 7 days for screening purposes

i. Pulse rate, systolic and diastolic blood pressure, respiration rate, pulse oxygen saturation and temperature. Blood pressure should also be measured at the clinic weekly during the first 4 weeks of treatment, and every 2 weeks from Week 4 to Week 8 and every 4 weeks thereafter. Daily home blood pressure monitoring is required via patient self-monitoring. Patients are required to check their blood pressure twice daily for at least the first 8 weeks after starting study treatment, or, if antihypertensive management is required, until a stable anti-hypertensive regimen has been established, even if this requires more than 8 weeks. After 8 weeks or once a stable regimen has been achieved, blood pressure monitoring may be reduced to once daily. Daily blood pressure monitoring is required for as long as the patient remains on cediranib treatment and for 30 days after cediranib discontinuation, or until the FPV. Daily blood pressure monitoring by the patient will be recorded using a handheld electronic device See Section 5.2.4.1.

j. Required at baseline, at every 8 weeks, until treatment discontinuation and at the 30-day safety follow-up visit, or until the FPV.

k. ECGs are required within 7 days prior to starting IPs, and when clinically indicated thereafter. Any clinically significant changes on all other visits should be recorded as adverse events.

l. Required for women of childbearing potential within 7 days prior to the start of IPs, every 4 weeks thereafter during study treatment. Pregnancy test for women of childbearing potential is required at the FPV and every 4 weeks thereafter until treatment discontinuation.

m. Left Ventricular Ejection Fraction required for patients with prior treatment with anthracyclines, or prior treatment with trastuzumab or central thoracic radiation therapy (RT) including exposure of heart to therapeutic doses of ionizing RT, history of myocardial infarction within 6-12 months prior to enrolment or history of other significant impaired cardiac function. For these patients LVEF will be done at screening and thereafter as clinically indicated, and per recommendations following review of initial safety data by the sponsor (see Table 16).

n. At screening, UPC ≤ 1, OR proteinuria ≤2+ on two consecutive dipsticks taken no less than 1 week apart, is required. Patients with 2+ proteinuria on dipstick must also have UPC < 0.5 on 2 consecutive samples. Refer to Section 5.2.1.4 for information on management of patients with potential nephrotic syndrome.

o. Repeat assessment not required on Day 1, if already performed during previous 7 days for screening purposes.

p. Full Blood Count as per Section 5.2.1.1: hemoglobin, platelets, mean cell volume, white blood cell count, absolute neutrophil count and absolute Lymphocyte count

q. Biochemistry (sodium, magnesium, calcium, potassium, albumin, total protein, creatinine, total bilirubin, ALT, AST, alkaline phosphatase). Creatinine clearance (Cockcroft-Gault or another validated method); to be calculated at baseline and re-calculated as clinically indicated during study conduct.

r. Baseline tumor assessment should include CT/MRI of the chest, abdomen and pelvis. Follow-up CT/ MRI tumor assessments will cover chest (in those patients with disease in the chest or upper abdomen lymphadenopathy at baseline), abdomen and pelvis. Any other sites at which new disease is suspected should also be appropriately imaged. Baseline radiological imaging is required within 4 weeks prior to first dose of investigational products (IPs). Follow up assessments should be done every 8 weeks after first dose of IP until objective radiological disease progression, withdrawal of consent or the primary analysis.

s. Blood samples for PBMC testing (8 mL) and plasma biomarker testing (6 mL) will be taken at baseline; at Week 4; at Week 8 and treatment discontinuation. Details to be found in the lab manual.

t. Eight PK samples per patient (4 samples for cediranib and 4 samples for olaparib) will be collected at steady state: 2 samples on Week 4 and 2 samples on Week 8 visit for cediranib and olaparib each. At the Week 4 visit, the first 2 samples should be taken 0.5 hours prior to the first dose of cediranib at the Week 4 visit; the second 2 samples should be taken 1 to 3 hours after the first dose of olaparib at the Week 4 visit. At the Week 8 visit, 2 samples should be taken 0.5 hours prior to the dose of cediranib administration; the second 2 samples should be taken 1 to 3 hours after the first dose of olaparib at the Week 8 visit.

u. Assessments for survival should be made every 8 weeks (relative to first dose) following objective disease progression. Survival information may be obtained via telephone contact with the patient, patient's family or by contact with the patient's current physician. Subsequent anticancer therapies should also be recorded. Patients should be contacted or other data sources checked (see Section 3.10.2) in the 2 weeks following the data cut-off for the primary analysis to provide current complete survival data.

v. Missed doses of study medications will be reported by patients using a handheld electronic device. These data will be reviewed by the Investigator at each patient visit and data entered in eCRF.

Abbreviations: AE adverse event; ALT alanine transferase; AST aspartate transferase; *BRCA* breast cancer resistance protein; CA-125 cancer antigen-125; CT computed tomography; ctDNA circulating tumor DNA; ECG electrocardiogram; ECOG Eastern Cooperative Oncology Group; eCRF electronic case report form; EORTC European Organization for Research and Treatment of Cancer; FPV final protocol visit; FT4 free thyroxine; IP investigational product; LVEF left ventricular ejection fraction; MRI magnetic resonance imaging; N/A not available; PBMC peripheral blood mononuclear cells; PK pharmacokinetics; PRO-CTCAE Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; QLQ quality of life questionnaire; SAE serious adverse event; TSH thyroid stimulating hormone; UPC urine protein:creatinine ratio.

4.1 Screening/Enrollment period

Prior to inclusion into the study, patients will undergo screening. All patients must sign the Informed Consent Form and if applicable, any locally required privacy act document authorization must also be obtained prior to the start of any screening procedures. All screening procedures must be performed within 28 days before dosing (Day -28 to Day -1).

Consenting patients are assessed (Table 5) to ensure that they meet eligibility criteria and to discontinue other therapies, if required (Section 3.1, Section 3.4). Patients who do not meet these criteria must not be entered into the study.

All patients agree to provide a sample of their archival FFPE tumor sample (or approximately 20 unstained sections mounted on glass slides prepared from the block) from the primary or recurrent cancer for entry into this study, and a blood sample which may be used for a subsequent confirmatory *BRCA* mutation test using the Myriad BRACAnalysis CDx® test. If archival tumor sample is not available tumor sample from fresh biopsy is acceptable.

4.2 Treatment period

Descriptions of the procedures for this period are included in the Schedule of Assessments (Table 5) with exceptions of the following specific requirements for the treatment period:

The Study conduct period starts at the time of administration of the first dose of IPs (cediranib plus olaparib). There is no maximum duration for taking IPs in this study.

While on study treatment, patients will be required to attend study visits every week during the first 4 weeks, every 2 weeks during the next 4 weeks and every 4 weeks (± 3 days) thereafter. RECIST assessments will be performed every 8 weeks (±1 week) after first doses of IPs until disease progression. Patients will continue the study treatments until:

- objective radiological disease progression, as defined by RECIST 1.1 guidelines,
- unacceptable toxicity or
- discontinuation of IPs for other reasons (patient withdrawal of consent, physician discretion; see Section 3.9, Section 3.10 and Section 3.11).
- Severe non-compliance with the protocol.

4.3 Follow-up period

If both study treatments are discontinued, patients should undergo the assessments required at the discontinuation visit (see Table 5), whether or not radiological disease progression has occurred. A safety follow-up visit should be conducted 30 days after the discontinuation visit. Any serious and/or non-serious AEs ongoing at this time should be followed-up to resolution or until, in the Investigator's opinion, the condition is unlikely to improve or resolve due to

the patient's underlying disease. Descriptions of the procedures for the follow-up visit are included in the Schedule of Assessment (Table 5).

Assessments in the post study treatments follow-up period (following discontinuation of IPs), depend on whether a patient discontinues study treatments in the presence or absence of radiological disease progression.

4.3.1 Discontinuation of study treatments due to disease progression

If a patient discontinues IPs because of radiological disease progression, she will be followed up for survival every 8 weeks (relative to first dose). Survival information may be obtained via telephone contact with the patient, patient's family or by contact with the patient's current physician.

4.3.2 Discontinuation of study treatments in the absence of disease progression

If a patient discontinues IPs in the absence of radiological disease progression, RECIST assessments for disease progression should continue to be performed every 8 weeks (±1 week) until radiological disease progression or withdrawal of consent. Once a patient has radiological disease progression, she will be followed up as described in Section 4.3.1 above.

Once patients have been discontinued from the IPs, other treatment options will be at the discretion of the Investigator. All subsequent anti-cancer treatments should be recorded according to Section 7.8. If the patient is lost to follow-up, then this should be noted in the eCRF.

4.4 Final protocol visit

Patients who continue to receive clinical benefit without meeting any discontinuation criteria during the study, will complete a FPV which will occur at their last scheduled visit prior to data cut-off for the primary analysis. Beyond the FPV, patients may continue to receive cediranib and/or olaparib if they are deriving clinical benefit in the opinion of the investigator, and not fulfilling any discontinuation criteria.

Beyond the FPV, patients continuing to receive IPs are to be treated as described in Section 4.5.

4.5 End of study

The end of the study is defined as 'the last visit of the last patient undergoing the study' (ie, last subject last visit [LSLV]) or when the Sponsor decides to discontinue the study.

There will be a primary data cut-off defined at approximately 8 months (LSLV) after the last patient received her first dose of study treatment. This primary data cut-off will be followed by clinical database lock when all data for all patients have been collected. The primary data analysis will be performed and a Clinical Study Report (CSR) written based on this data set.

Patients who continue to receive clinical benefit without meeting any discontinuation criteria during the study, will complete a FPV which will occur at their last scheduled visit prior to primary data cut-off. Beyond the FPV, patients may continue to receive cediranib and/or olaparib (to be provided by the Sponsor), if they are deriving clinical benefit in the opinion of the investigator, and not fulfilling any discontinuation criteria.

Such patients are to be followed in accordance with the Medical Standard of Care and as deemed appropriate by the Investigators. Serious adverse event reporting (on paper) will continue to ensure safety data collection and monitoring of the patients while receiving the investigational product. It is recommended that investigators continue to observe ongoing patients at the frequency employed prior to the FPV. Protocol dose modification and stopping criteria are to be followed while a patient is receiving cediranib and/or olaparib. Restrictions regarding concomitant medications (Section 7.7) must be followed while the patient is receiving cediranib and/or olaparib. A change in the dose/schedule of cediranib and/or olaparib should only occur for safety reasons, based on the Investigator's judgement, and should generally follow the approach for dose reduction and discontinuation as described in this protocol. Combining cediranib and/or olaparib with other anti-cancer therapy is not allowed.

If in the opinion of the investigator, a patient is no longer receiving clinical benefit from the IPs beyond the FPV, then the IPs will be stopped. The Investigator will inform AstraZeneca when a patient discontinues the IPs. Patients must return unused medication during routine clinic visits; drug accountability information must continue to be collected in patient source documents until the patient discontinues treatment. Patients will continue to be monitored for all SAEs and pregnancies while receiving IPs and for 30 days after the last dose of IPs.

5. STUDY ASSESSMENTS

The RAVE Web Based Data Capture (WBDC) system will be used for data collection. The investigator will ensure that data are recorded on the eCRFs as specified in the study protocol and in accordance with the eCRF completion guidelines.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded in the eCRF and 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.

5.1 Efficacy assessments

5.1.1 Tumor assessments by CT or MRI scans

Radiological assessment should use the same modality of imaging throughout the trial. Contrast-enhanced CT scan is preferred but MRI is acceptable where CT is contraindicated. Please refer to the Image Acquisition Guidelines and Site Operations Manual for a quick reference guide for image acquisition and data handling.

Baseline tumor assessment should include CT/MRI of the chest, abdomen and pelvis within 28 days prior to the start of IPs. Follow-up CT/ MRI tumor assessments will cover chest (in those patients with disease in the chest or upper abdomen lymphadenopathy at baseline), abdomen and pelvis with any other regions imaged at baseline where disease was present. Any other sites at which new disease is suspected should also be appropriately imaged. Radiological examinations performed in the conduct of this study should be retained at site as source data. Copies of all imaging assessments including unscheduled visit scans will be collected on an ongoing basis and sent to Contract Research Organization (CRO) for ICR (see Section 5.1.3).

All treatment decisions will be based on Investigator assessment of scans. All patients will have RECIST 1.1 tumor assessments at screening (within 28 days prior to the date of first dose of IPs) and thereafter every 8 weeks (±1 week) relative to the date of first dose of IPs (Table 5) until objective radiological disease progression as defined by RECIST 1.1 and as determined by the Investigator, or unless they withdraw consent. Objective radiological response on treatment (CR or PR) will need to be confirmed during next RECIST 1.1 visit assessment.

If a patient discontinues IPs for any reason other than disease progression or withdrawal of consent, RECIST 1.1 assessments should continue as per protocol schedule until evidence of objective radiological progression or withdrawal of consent (see Section 4.3).

It is important to follow the assessment schedule as closely as possible. If scans are performed outside of scheduled visit (±1 week window) and the patient has not progressed, every attempt should be made to perform the subsequent scans at their scheduled time points.

5.1.2 Tumor evaluation

RECIST 1.1 will be used to assess progression and patient response to treatment by determining ORR, DCR, DoR and PFS. The RECIST 1.1 guidelines for measurable, non-measurable, target and non-target lesions (NTLs) and the objective tumor response criteria (CR, PR, SD or PD) are presented in Appendix F.

Categorization of objective tumor response assessment will be based on the RECIST 1.1 criteria of response: CR, PR, SD or PD. Target lesion progression will be calculated in comparison with when the tumor burden was at a minimum (ie, smallest sum of diameters previously recorded on study). In the absence of progression, tumor response (CR, PR, or SD) will be calculated in comparison with the baseline tumor measurements obtained before starting treatment. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST 1.1 criteria. For this study, a rise in CA-125 alone is not sufficient to declare progression, and progression events should be determined by radiographic evidence of progression.

If the Investigator is in doubt as to whether progression has occurred, particularly with response to NTLs or the appearance of a new lesion, it is advisable to continue treatment until

the next scheduled assessment or sooner if clinically indicated and reassess the patient's status. If repeat scans confirm progression, then the date of the initial scan should be declared as the date of progression.

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

5.1.3 Central reading of scans

An independent review of all scans used in the assessment of tumors using RECIST 1.1 will be conducted. Copies of all imaging assessments including unscheduled visit scans will be collected on an ongoing basis and sent to an AstraZeneca appointed CRO for central analysis. If a patient had tumor biopsy during screening, but after the baseline RECIST scan, information on which lesion was biopsied will be provided to ICR so that such lesion is not chosen as the target lesion. Results of this independent review will not be communicated to Investigators, and the management of patients will be based solely upon the results of the RECIST assessment conducted by the Investigator. The primary analysis of ORR will be based on ICR assessment.

5.1.4 Survival assessment

Assessments for survival should be made every 8 weeks (relative to first dose) following objective disease progression or discontinuation from treatment. Survival information may be obtained via telephone contact with the patient, patient's family or by contact with the patient's current physician. OS will be analyzed at the time of the primary analysis; patients should be contacted or other data sources checked (see Section 3.10.2) in the 2 weeks following the data cut-off for the primary analysis to provide current complete survival data. Subsequent anti-cancer therapies should also be recorded.

5.2 Safety assessments

5.2.1 Laboratory safety assessments

Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis will be taken at the times indicated in the Schedule of Assessments (see Section 4).

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, hematology 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:

5.2.1.1 Full hematology assessments for safety

- Hemoglobin (Hb)
- Platelets
- Mean cell volume (MCV)
- White blood cell count (WBC)
- Absolute neutrophil count (ANC)
- Absolute lymphocyte count.

5.2.1.2 Biochemistry assessments for safety

- Sodium
- Potassium
- Calcium
- Magnesium
- Creatinine
- Total bilirubin
- Alkaline phosphatase [ALP]
- Aspartate transaminase [AST]
- Alanine transaminase [ALT]
- Total protein
- Albumin

In addition, samples for the measurement of thyroid stimulating hormone (TSH) and free thyroxine (FT4) are to be collected at screening, every 8 weeks during the treatment period, and for patients continuing to receive clinical benefit without meeting any discontinuation criteria during the study, at the FPV. The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at center as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported, see Section 6.3.

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

5.2.1.3 Disease specific tumor marker samples (CA-125)

As part of the routine blood samples, all patients will have CA-125 assessment at screening, every 8 weeks during the treatment period, and at study treatment discontinuation.

A rise in CA-125 alone is not sufficient to declare progression, and discontinue IPs; progression events should be determined by radiographic evidence of progression, see Section 5.1.2.

Further assessment of CA 125 post radiological progression will be at the discretion of the investigator according to local clinical practice.

For blood volume see Section 5.8.1.

5.2.1.4 Urinalysis

Urinalysis by dipstick should be performed as stated in Schedule of Assessments in Table 5. Microscopic analysis should be performed by the hospital's local laboratory if required. If appropriate, a spot urine protein-creatinine ratio may be performed.

Patient with urine protein ≥3.5 g/24 hours (CTCAE Grade 3 according to CTCAE v4) or urinary protein/creatinine ratio of >3.5 should be considered as nephrotic-range proteinuria. Following identification of nephrotic range proteinuria, the following steps should be taken to explore if the patient has a nephrotic syndrome:

- Confirm if the patient had a normal renal function at baseline (creatinine ≤ULN)
- Check if the patient has reported any of the following as a treatment-emergent and concurrent AE: hypoalbuminemia (laboratory value albumin <3 g/dL, or an AE of hypoalbuminemia CTCAE Grade ≥ 2); edema (any); dyslipidemia (hypercholesterolemia, hypertriglyceridemia); hyperlipidemia; or a thrombotic event.

A specific safety questionnaire will be sent to the reporting Investigator, requesting detailed information, about patients who reported a nephrotic syndrome.

5.2.1.5 Bone marrow or blood cytogenetic samples

Bone marrow or blood cytogenetic samples may be collected for patients with prolonged hematological 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 eCRF.

5.2.2 Physical examination

A complete physical examination as per standard clinical practice should be performed by the Investigator at baseline, every 4 weeks during the treatment period, at the 30-day safety follow-up visit and, for patients continuing to receive clinical benefit without meeting any discontinuation criteria during the study, at the FPV. If there are any clinically significant abnormal findings not related to disease progression, they should be recorded as an AE on the eCRF. Height will be assessed at screening only. Weight will be assessed at baseline, at every 4 weeks during the treatment period, at the 30-day safety follow-up visit and, for patients continuing to receive clinical benefit without meeting any discontinuation criteria during the study, at the FPV.

5.2.3 ECG

5.2.3.1 Resting 12-lead ECG

ECGs are required within 7 days prior to starting IPs, and when clinically indicated thereafter.

Twelve-lead ECGs will be obtained after the patient has been rested in a supine position for at least 5 minutes in each case. 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 at baseline, the Investigator should record this in the baseline eCRF. If there is a treatment emergent significant abnormal finding, the Investigator will record it as an AE on the eCRF. The original ECG traces must be stored in the patient medical record as source data.

5.2.4 Vital signs

Any clinically significant changes in vital signs should be recorded as an AE. 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

Since rapid changes in BP can occur with cediranib treatment with the potential for life-threatening complications if hypertension is not appropriately managed, all patients should check their BP twice daily for at least the first 8 weeks after starting IPs, or, if antihypertensive management is required, until a stable anti-hypertensive regimen has been established, even if this requires more than 8 weeks. After 8 weeks or once a stable regimen has been achieved, BP monitoring may be reduced to once daily. Twice daily monitoring should be re-implemented after any cediranib dose interruption for at least two weeks or until the patient is re-established on a stable antihypertensive regimen, whichever takes longer.

Patients should continue to check their BP for as long as they remain on cediranib treatment and for 30 days after cediranib discontinuation. Patients will record their BP data using handheld electronic devices, to be provided by the study Sponsor.

Patient BP will be measured during routine study visits: weekly during the first 4 weeks, every 2 weeks during the next 4 weeks and every 4 weeks thereafter to ensure that BP guidelines are being correctly followed. During routine study visits, BP and pulse rate will be measured preferably using a semi-automatic BP recording device with an appropriate cuff size after 10 minutes rest. For timings of assessments refer to the Schedule of Assessments (see Table 5).

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

5.2.4.2 Body temperature

Body temperature will be measured in degrees Celsius according to local practice at the times indicated in the Schedule of Assessments (see Table 5; vital signs).

The date of collection and measurement will be recorded on the appropriate 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 only for pre-menopausal women of childbearing potential, within 7 days prior to the start of IPs, every 4 weeks thereafter during study treatment. Pregnancy test for women of childbearing potential is required at the FPV and every 4 weeks thereafter until treatment discontinuation. Tests will be performed by the hospital's local laboratory. If results are positive the patient is ineligible and must not be recruited into the study. A confirmed pregnancy during the study conduct must be recorded in eCRF and immediately reported; the patient will be discontinued from the IPs, but should continue in the study.

5.3 Other assessments

5.3.1 Clinical Outcome Assessments

PROs is an umbrella term referring to all outcomes and symptoms that are directly reported by the patient. PROs have become a significant endpoint when evaluating effectiveness of treatments in clinical trials. The following PROs will be administered: European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ)-C30, QLQ OV28, and Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE; see Appendix K).

5.3.1.1 EORTC QLQ C30 and EORTC QLQ OV28

The EORTC QLQ-C30 was developed by the EORTC Quality of Life Group 1993. It consists of 30 items and measures cancer patients' functioning health-related quality of life (HRQoL) and symptoms (Aaronson et al 1993) for all cancer types. Questions can be grouped into 5

multi-item functional scales (physical, role, emotional, cognitive and social); 3 multi-item symptom scales (fatigue, pain, nausea and vomiting); a 2-item global HRQoL scale; 5 single items assessing additional symptoms commonly reported by cancer patients (dyspnea, loss of appetite, insomnia, constipation, diarrhea) and 1 item on the financial impact of the disease.

The QLQ-OV28 is a module which is specific for ovarian cancer. It consists of 28 items assessing abdominal/GI symptoms (6 items), peripheral neuropathy (2 items), other chemotherapy side effects (5 items), hormonal symptoms (2 items), body image (2 items), attitudes to disease/treatment (3 items), sexuality (4 items), and four other single items.

5.3.1.2 PRO-CTCAE

The Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) system has been developed by the NCI. PRO-CTCAE is an item-bank of symptoms experienced by patients while undergoing treatment of their cancer. It was developed in recognition that collecting symptom data directly from patients using PRO tools can improve the accuracy and efficiency of symptomatic AE data collection. This was based on findings from multiple studies demonstrating that physicians and nurses underestimate symptom onset, frequency, and severity in comparison with patient ratings (Basch et al 2009; Basch et al 2014; Litwin et al 1999; Sprangers and Aaronson 1992). To date, 81 symptoms of the CTCAE (version 4) have been identified to be amenable to patient reporting. These symptoms have been converted to patient terms (eg, CTCAE term “myalgia” converted to “aching muscles”). For several symptoms, like fatigue and pain, additional questions are asked about symptom frequency, severity, and interference with usual activities. For other symptoms like rash, additional questions focus on the presence on the body. The items included in the PRO-CTCAE have undergone extensive qualitative review among experts and patients. These items and the additional questions for some of the symptoms have been extensively evaluated by cancer patients, using cognitive testing methods, to be clear, comprehendible, and measure the symptom of interest. Not all items are administered in any one clinical trial. The intention is to only ask patients to complete those items which are considered relevant for the trial, site of cancer, and cancer treatment (see Appendix K). The following 6 PRO-CTCAE AEs will be collected in the study: nausea, vomiting, diarrhea, decreased appetite, fatigue, and dizziness. In addition to these items from the PRO-CTCAE item bank, the following additional item will be asked together with the PRO-CTCAE items: "In the last 7 days, how much did LOOSE OR WATERY STOOLS (DIARRHEA) INTERFERE with your usual or daily activities?"

5.3.1.3 Administration of PRO questionnaires

Patients will complete the PRO assessments at home and at site using the same handheld electronic device (ePRO).

All assessments should be completed according to the following parameters:

- Without assistance from site staff or anyone else according to the assessment schedule (see Table 5)

- Before any other study procedures are conducted at a given visit
- Before being seen by a study nurse or physician

Each center must allocate the responsibility for the administration of the ePROs to a specific individual (eg, a research nurse or study coordinator) and, if possible, assign a backup person to cover if that individual is absent. Subjects may complete some of the ePROs at study sites if the assessment time point coincides with a scheduled site visit; otherwise, subjects may complete the ePROs at home. Similarly, during the post-progression period, subjects should complete ePROs at home or at the study site if a scheduled visit coincides with the time point. If subjects have had scans or other tests at an outside facility or missed a scheduled data collection site visit, ePROs should still be completed by the subject at home for that scheduled visit within the window period.

The Investigator will arrange for relevant training in the set-up of the electronic device and training patients in how to self-administer the questionnaires using the electronic device. Subjects should complete the questionnaires in accordance with the study schedule (see Table 5).

The significance and relevance of the data should be explained carefully to participating subjects so that they are motivated to comply with data collection. Reminders should be sent to subjects at home as needed to ensure compliance with the assessment schedules.

The following best practice guidelines should be followed when collecting PRO data via an electronic device:

- PRO questionnaires must be completed prior to any other study procedures (following informed consent) and before discussion of disease progression to avoid bias in patient's responses to the questions.
- When each instrument is due to be completed, the following order for completion should be ensured: EORTC-QLQ-C30, EORTC-QLQ-OV28, PRO-CTCAE.
- PRO questionnaires must be completed by the subject in private.
- The research nurse or appointed site staff must explain to subject the value and relevance of study participation and inform them that these questions are being asked to find out, directly from them, how they feel. The research nurse or appointed site staff should also stress that the information is confidential. Therefore, if the subjects have any medical problems, they should discuss them with the doctor or research nurse separately from the ePRO assessment.
- The research nurse or appointed site staff must train the subject on how to use the ePRO device, using the materials and training provided by the

ePRO vendor, and provide guidance on whom to call if there are problems with the device if the patient is completing the ePRO at home.

- The research nurse or appointed site staff should remind subjects that there are no right or wrong answers.
- The research nurse or appointed staff must avoid clarifying items in order to avoid bias.
- The subject must not receive help from relatives, friends, or clinic staff to answer the PRO questionnaires. If a subject uses visual aids (eg, spectacles or contact lenses) for reading and does not have them when he attends the clinic, the subject will be exempted from completing the PROs.
- Site staff must not read or complete the PRO questionnaires on behalf of the subject. If the subject is unable to read the questionnaire (eg, is blind or illiterate), that subject is exempted from completing PRO questionnaires and may still participate in the study. Subjects exempted in this regard should be flagged appropriately by the site staff.
- The subject should be given sufficient time to complete the PRO questionnaires at her own speed.

The research nurse or appointed site staff must monitor compliance to ensure all data is captured. Compliance must be checked at each study visit to identify problems early. If a subject's compliance drops below 85%, they will be flagged in the routine compliance report generated by the ePRO system and a check-in call from the site to ask the subject if she has any difficulties is highly recommended.

5.3.2 Exploratory Immunologic/Molecular Assessments

Assessment of somatic deleterious or suspected deleterious variant in *BRCA* genes (*BRCA1* or *BRCA2*) or in HRR-associated genes, and potential homologous recombination deficiency (HRD), including genomic scarring, *BRCA1* methylation, and other genes that might modify HRD, using current and/or potential future tumor based assays including, but not limited to, *BRCA* or HRR gene mutations may be carried out.

Markers of different T-cell populations and phenotypes of myeloid-derived suppressor cells and immune suppressive monocytes in peripheral blood mononuclear cells (PBMCs), including, but not limited to, the combination of cell-surface markers CD3, CD4, CD8, CD11, CD14, CD19, CD25, CD33, CD45, CD56, Foxp3, HLA-DR, TIM-3, PD1 and CTLA-4, will be analyzed by fluorescence activated cell sorter (FACS) analysis and/or mRNA analysis.

Assessment of biomarkers such as VEGF-A, C, D; sVEGFR2, Tie2, Ang1, 2, leptin and interleukin 6 (IL6), will be carried out to define the angiogenic and inflammatory biomarker profile.

Sequencing of circulating tumor DNA (ctDNA) may also be conducted, to identify tumor-derived mutations.

5.4 Pharmacokinetics

5.4.1 Collection of samples

Blood samples for determination of cediranib and olaparib concentrations in plasma will be taken at the times presented in the schedule of assessments Table 5. Samples will be collected, labelled stored and shipped as detailed in the Laboratory Manual.

5.4.2 Determination of drug concentration

Samples for determination of cediranib and olaparib concentrations in plasma will be analyzed by Covance on behalf of AstraZeneca, using appropriate bioanalytical methods.

5.4.3 Storage and destruction of PK samples

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

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

5.5 Pharmacodynamics

Pharmacodynamic samples will not be taken during the study.

5.6 Genetics

Genetic samples will not be taken during the study.

5.7 Biomarker analysis

Key biomarker data will be reported in the main CSR.

5.7.1 Collection of blood sample for Myriad germline *BRCA* testing

All patients must have no evidence of deleterious or suspected deleterious germline mutation(s) in their *BRCA1* or *BRCA2* genes to be enrolled in the study. *BRCA1* and/or *BRCA2* variants that are classified as “Variants of uncertain clinical significance” or “VUS” are eligible, as well as “Variant, favor polymorphism” or “benign polymorphism”. Germline *BRCA* status may be assessed as part of the screening procedure for the study (via Myriad

BRACAnalysis CDx®); or, patients may be entered into the study on the basis of a local test conducted in an appropriately accredited laboratory (eg, CLIA-certified) that includes comprehensive DNA sequencing and large rearrangement analysis of *BRCA1* and *BRCA2*.

For patients that can be enter the study on the basis of a pre-existing known *gBRCA* status by a local test conducted in an appropriately accredited laboratory, a blood sample must be taken once the patient has consented to the study which may be used for a subsequent confirmatory *BRCA* mutation test using Myriad's BRACAnalysis CDx® test.

For patients who meet the trial eligibility criteria, but do not know their *BRCA* mutation status, or whose *gBRCA* status was determined using a local test conducted in a local laboratory which was not appropriately accredited laboratory, or where the *BRCA* test result is non-mutant but did not include comprehensive sequencing and large rearrangement analysis of *BRCA1* and *BRCA2*, a blood sample for the Myriad *BRCA* test can be taken once all local ethical procedures (eg, genetic counselling) for such testing have been completed. When the result from the Myriad BRACAnalysis CDx® test indicates the patient has no evidence of a deleterious or suspected deleterious germline mutation in *BRCA1* or *BRCA2* genes, the patient can be entered into the study.

Residual blood (or its derivatives) may be used to develop and validate future *BRCA* companion diagnostic tests and for additional exploratory work, to elucidate the mechanism of response, understand the mode of action of study treatment, and improve the understanding of disease recurrence.

5.7.2 Collection of biomarkers biological samples

Biological samples (archived tumor samples and blood samples) will be collected only from patients who are eligible to start study treatment and will be analyzed for exploratory biomarkers to assess correlations with disease activity, effects of study drug, clinical outcomes and toxicity:

- Mandatory: Archival tumor sample or fresh tumor biopsy

– FFPE tumor sample from the primary or recurrent cancer must be available for central testing (or approximately 20 unstained sections mounted on glass slides prepared from the block). If there is not written confirmation of the availability of an archival tumor sample prior to enrollment, or if the patient does not consent to donating a fresh tumor biopsy sample (if an archival sample is unavailable), the patient is not eligible for the study. The tumor samples will be collected and will be analyzed for somatic deleterious or suspected deleterious variants in *BRCA1* or *BRCA2* genes, and the following HRR-associated genes: *ATM, BRIP1, PALB2, RAD51C, BARD1, CDK12, CHEK1, CHEK2, FANCL, PPP2R2A, RAD51B, RAD51D,* and *RAD54L*, to assess correlations with disease activity, effects of study drug, clinical outcomes and toxicity.

- Mandatory: Blood sample for biomarker analysis

- Blood samples for PBMC testing (8 mL) and plasma biomarker testing (5 mL) will be collected from all patients at baseline; at Week 4; at Week 8 and at discontinuation of IPs, for exploratory biomarker work.

- Blood sample (10 mL) at baseline and at discontinuation of IPs to evaluate ctDNA.

5.7.3 Storage, re-use and destruction of biological samples

Samples will be stored for a maximum of 15 years from the date of LSLV (ie, approximately 12 months after the last patient received her first dose of IP) 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.

5.7.4 Labelling and shipment of biological samples

The Investigator 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 C 'IATA 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.

5.7.5 Chain of custody of biological samples

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

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

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

AstraZeneca 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.

5.7.6 Withdrawal of Informed Consent for donated biological samples

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

If the patient withdraws consent for the collection of the mandatory biological samples that are an integral part of the study (ie, the archival tumor sample or the mandatory biomarker blood samples), further study participation can be continued, if the patient is already receiving treatment with IPs.

The PI:

- 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 laboratory(ies) 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 central laboratory(ies) 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.

5.8 Biological sampling procedures

5.8.1 Volume of blood

The volume of blood that will be drawn from each patient will vary, dependent upon the length of time that the patient remains in the trial. However, the volume of blood to be drawn from each patient (including for PK samples) during screening and up to and including Week 8 should not exceed 154 mL, according to National Institutes of Health (NIH) guidance (NIH guidance 2009).

The total volume of blood to be drawn from each patient in the study, assuming they complete screening, 48 weeks of treatment, a treatment discontinuation visit and the 30-day follow-up visit, should not exceed 335 mL.

The procedures for the collection, handling, and shipping of laboratory samples are specified in the Sample Handling and Logistics Manual supplied to sites.

Safety laboratory assessments will be performed locally by means of their established methods. The number of samples/blood volumes is therefore subject to site-specific change.

Extra blood samples may also be collected if, for example, additional samples are required for repeat safety assessments.

The estimated total volume of blood that will be drawn from each patient in this study is as shown in Table 6.

Table 6 Estimated maximum volume of blood to be drawn from each patient

Assessment		Sample volume (mL)	No. of samples - Screening	No. of samples Day 1 to Week 8	Every 4 weeks (Week 8 to treatments discontinuation)	Treatments Discontinuation visit	30 day follow-up visit	Final Protocol Visit
Whole Blood sample: • Prospective Myriad BRACAnalysis CDx® test for patients with unknown *BRCA* status or potential retrospective analysis in patients with a local test result		9	1					
Blood sample for ctDNA		10	1			1		
Blood samples (PBMC) for biomarker analysis		8	1	2		1		
Blood samples (plasma) for biomarker analysis		6	1	2		1		
Safety	Clinical chemistry (locally assessed)	5	1	5	1	1	1	1
	Hematology (locally assessed)	5	1	5	1	1	1	1
Blood sample for CA-125 (locally assessed)		2	1	1	1	1	1	
Pharmacokinetic (Blood samples processed to plasma & frozen)		2 mL for cediranib + 2 mL for olaparib	0	8				
Total volume (mL)			55	112	12	36	12	10

Abbreviations: *BRCA* breast cancer susceptibility gene; CA-125 cancer antigen-125; ctDNA circulating tumor deoxyribonucleic acid; PBMC Peripheral blood mononuclear cell; PK Pharmacokinetics.

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 adverse events

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, ECG). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no IPs have been administered.

The term AE is used to include both serious and non-serious AEs.

6.1.1 Adverse Events of Special Interest

Adverse events of special interest (AESIs) are events of scientific and medical interest specific to the further understanding of the safety profiles of cediranib and olaparib; AESIs require close monitoring and rapid communication by the investigators to AstraZeneca. An AESI may be serious or non-serious.

- AESIs for cediranib are the Important Identified Risks: PRES, arterial thromboembolic events, and the Important Potential Risks: symptomatic left ventricular dysfunction and cardiac failure; nephrotic syndrome; renal thrombotic microangiopathy and liver failure.

- AESIs for olaparib are the Important Potential Risks of MDS/AML, new primary malignancy (other than MDS/AML) and pneumonitis.

6.2 Definitions of serious adverse event

An SAE is an AE occurring during any study phase that fulfils one or more of the following criteria:

- Results in death (NOTE: death is an outcome, not an event)

- Is immediately life-threatening (NOTE: the term “Life-Threatening” refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused a death had it been more severe)

- Requires in-patient hospitalization or prolongation of existing hospitalization

- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of a SAE, see Appendix B to the Clinical Study Protocol. The full requirements of the ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2 will be adhered to.

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

SAEs will be collected from time of signature of informed consent throughout the treatment period up to and including the 30-day follow-up period. AEs will be collected between the date of the first dose of IPs and the end of the 30-day follow-up period. All ongoing and any new AEs/SAEs identified during the 30 calendar days follow up period, after the last dose of IPs must be followed to resolution, unless resolution is unlikely to occur.

6.3.2 Follow-up of unresolved adverse events

Any SAE or non-serious adverse event 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 Adverse events after the 30 day follow up period

For olaparib pharmacovigilance purposes and characterization of events of special interest, 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. These AEs must be reported according to the timelines for reporting an SAE (see Section 6.4). 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. A questionnaire will be sent to any investigator reporting MDS/AML, pneumonitis, or new primary malignancy as an aid to provide detailed information on the case.

At any time after a patient has completed the study, if an Investigator learns of any SAE or death, unrelated to SAEs of special interest, and he/she considers there is a reasonable possibility that the event is causally related to the IPs, the Investigator should notify AstraZeneca, Patient Safety.

Patients who are gaining clinical benefit in the opinion of the Investigator are allowed to continue IPs post FPV and all SAEs must continue to be collected and reported to Patient Safety within the usual timeframe.

Otherwise, after end of study 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).

6.3.4 Variables

The following variables will be collected for each AE;

- AE verbatim
- The date when the AE started and stopped
- Changes in CTCAE grade will be reported for AEs of diarrhea, fatigue, hypertension and nausea. For all other AEs, only the highest attained CTCAE grade will be reported.
- Whether the AE is serious or not
- Investigator causality assessment against each of the IP(s) (yes or no)
- Action taken with regard to each of the IP(s)
- Outcome (if resolved with sequelae then sequelae should be recorded).

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

- Date AE met criteria for SAE
- Date Investigator became aware of SAE
- AE seriousness criteria (see Section 6.2)
- If the patient was hospitalized:
  - Date of hospitalization
  - Date of discharge

The following variables will also be collected for deaths:

- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to IPs and/or Study procedure(s).

Investigators are also required to complete targeted safety questionnaires should any of the following events be reported: MDS/AML, new primary malignancy or pneumonitis.

The grading scales found in the NCI CTCAE version 4.03 will be utilized 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 NCI CTCAE version 4.03 is available at http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.

Adverse events not listed by CTCAE version 4.03 will be graded using the following criteria:

Intensity rating scale:

1 mild (awareness of sign or symptom, but easily tolerated)

2 moderate (discomfort sufficient to cause interference with normal activities)

3 severe (incapacitating, with inability to perform normal activities)

Alternative intensity rating scale for in-patients:

4 mild (awareness of sign or symptom, but easily tolerated)

5 moderate (disturbing but still tolerable)

6 severe (intolerable).

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.

6.3.5 Causality collection

The Investigator will assess causal relationship between each 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 one or both components of the combination therapy?*'

Causality assessment for all AEs must be clearly assigned for each IP. Causal relationship will also be assessed for other (ie, other than one of study IPs) medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

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

6.3.6 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or care provider reported in response to the open question from the study personnel: '*Have you had any health problems since the previous visit/you were last asked*?', or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms; for example, for vomiting, nausea, fever, please consider providing diagnosis if available, as 1 AE of 'gastroenteritis' if appropriate, instead of 3 separate AEs. 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.

6.3.7 Adverse events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be summarized in the CSR. Deterioration as compared with baseline in protocol-mandated laboratory values, vital signs and ECG abnormalities should only be reported as AEs or SAEs if one of the following is met:

- Any criterion for an AE or SAE is fulfilled
- Causes discontinuation of IPs
- Causes IP interruption
- Causes IP dose reduction
- The abnormality is considered clinically significant by the Investigator

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (eg, anemia versus low Hb value). In the

absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters (ie, those not described in Table 5) should be reported as AE(s).

Deterioration of a baseline laboratory value or condition, 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.

6.3.8 Hy's Law

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

6.3.9 Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the IPs are being studied. It may be an increase in the severity of the disease under study and/or increases in the signs and 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.

6.3.10 New cancers

The development of a new primary cancer (including skin cancer) should be regarded as an AE and will generally meet at least one of the SAE criteria (see Section 6.2). New primary cancers are those that are not the primary reason for the administration of the IPs 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.

6.3.11 Lack of efficacy

When there is deterioration in the cancer, for which the IPs are being used, 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 IPs 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.

6.3.12 Deaths

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

- Death clearly the result of disease progression 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 a 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 a 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 serious adverse events

All SAEs have to be reported, whether or not considered causally related to the IPs, or to the study procedure(s). All SAEs will be recorded in the electronic case report form (eCRF).

For patients who continue to receive clinical benefit and IP after data cut-off, investigators will continue to report all SAEs to AstraZeneca Patient Safety until 30 days after study treatment is discontinued (Section 6.3.1). As the clinical study database will have closed, investigators should complete paper SAE forms and fax them directly to the AstraZeneca Patient Safety Data Entry site for entering onto the AstraZeneca Patient Safety database. Drug accountability should continue to be performed until the patient stops study treatment completely.

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 adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day 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 WBDC system, an automated email alert is sent to the designated AstraZeneca representative.

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

The AstraZeneca representative will be available between visits if the investigator(s) or staff at the center needs information or advice about the study conduct. AstraZeneca medical

personnel will be readily available to discuss study related medical questions or problems with the investigator(s). Contact details are provided separately in the Investigator Study File.

The reference documents for definition of expectedness/listedness are the IBs for cediranib and olaparib.

6.5 Overdose

The use of IPs in doses in excess of that specified in the protocol is considered to be an overdose.

Approximately 290 patients have received cediranib at dose levels of 45 mg or higher. At these higher dose levels the cediranib safety profile was similar to that observed at lower dose levels of 20 mg. In cases of suspected overdose, cediranib should be paused, BP monitored and if needed, supportive care instituted. There is no specific treatment for cediranib overdose. At the discretion of the Investigator, re-starting cediranib at the recommended dose can be considered.

There is currently no specific treatment in the event of an overdose with olaparib and possible symptoms of overdose are not established. In the event of an overdose, physicians should follow general supportive measures and AEs associated with overdose should be treated symptomatically. Any dose, or frequency of dosing, that exceeds the dose regimen specified in the study protocol should be reported as an overdose. The maximum tolerated dose is 300 mg bd for the tablet formulation.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE eCRF, including the Overdose section of the eCRF.
- An overdose without associated symptoms is only reported on the Overdose section of the eCRF.

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 a 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.

6.6.1 Maternal exposure

Women of childbearing potential must use any two highly effective forms of contraceptive methods in combination to avoid becoming pregnant while receiving IPs and for at least 6 weeks following the last dose of study treatments (cediranib + olaparib). The efficacy of hormonal contraceptives may be reduced if co-administered with cediranib (see Section 3.8); therefore, an additional non-hormonal contraceptive method should be used during treatment (see Appendix J) and pregnancy tests performed as required per SOA See Table 5). Should a pregnancy still occur, the IPs should be discontinued immediately and the pregnancy reported to AstraZeneca.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the IPs 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) occurring from the date of the first dose of study medication until 6 weeks after the last dose of study medication should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy 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 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 eCRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

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 recognized 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 subject
- 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 subject received the medication (excluding IVRS/IWRS errors)
- Wrong drug administered to subject (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
- Subject accidentally missed drug dose(s) eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Subject failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AZ product

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

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

The dose levels and the general approach to dose modification of the cediranib and olaparib component of the combination therapy are shown in Table 7 and Table 8, respectively. Specific dose modification information for some AEs are provided in Section 6.8.3 and Section 6.8.4. Please refer to the current IBs for emerging safety data for cediranib and olaparib; CCI [redacted] AEs should be treated with the appropriate maximum supportive care, and dose reductions should be clearly documented in the eCRF.

Table 7 Dose modification cediranib

Dose Level	Cediranib tablets
Initial dose	30 mg daily
Dose reduction 1	20 mg daily
Dose reduction 2	15 mg daily

Table 8 Dose modification of olaparib

Dose Level	Olaparib tablets
Initial dose	200 mg twice daily
Dose reduction 1	150 mg twice daily
Dose reduction 2	100 mg twice daily

At the discretion of the investigator, the study drugs may be held or dose modified independently if the observed toxicity is attributed to only one of the drugs, while the patient continues to receive the drug not associated with the observed toxicity. The time a given drug is held should not exceed 3 weeks. Once dose of study drug(s) have been reduced, no dose re-escalation is permitted.

If treatment has to discontinue due to toxicity, both IPs (cediranib and olaparib) should be discontinued at the same time; patients are not allowed to remain in the study if they are taking either cediranib or olaparib as monotherapy. However, in rare circumstances, patients experiencing ongoing clinical benefit but who develop one of the toxicities listed below related to one of the IPs that prevents them to continue to take this IP, may be allowed to continue on the unrelated drug if in the opinion of the treating investigator the risk benefit remains favorable and only after discussion with the AstraZeneca Study Physician and the Principal Investigator.

AEs requiring cediranib to be discontinued:

- GI perforation
- Arterial Thromboembolic Event
- PRES
- Severe hemorrhage
- Severe persistent hypertension despite maximal anti-hypertensive treatment

AEs requiring olaparib to be discontinued:

- Bone marrow findings consistent with MDS/ AML
- Severe persistent anemia
- Pneumonitis

Patients experiencing ongoing clinical benefit who experience a related AE where continuation of one of the drugs is considered, in the judgment of the treating Investigator AND the Principal Investigator, to be potentially life threatening or with the potential for long-term harm to the patient, may be allowed to continue on the unrelated drug after discussion with the AstraZeneca Study Physician and the Principal Investigator.

6.8.1 Hematologic toxicity

Management of neutropenia and thrombocytopenia

Neutropenia and thrombocytopenia are recognized common adverse drug reactions reported for both olaparib and cediranib. Treatment should be managed according to Table 9:

Table 9 Management of neutropenia or thrombocytopenia

	Olaparib dose	**Cediranib dose**
CTCAE Grade 1-2 ANC >1.0 G/L or Platelet count >50 G/L	Investigator judgement to continue treatment or allow dose interruption; dose interruptions should be for a maximum of 3 weeks; appropriate supportive treatment and causality investigation	Investigator judgement to continue treatment or allow dose interruption; dose interruptions should be for a maximum of 3 weeks; appropriate supportive treatment and causality investigation

Table 9 Management of neutropenia or thrombocytopenia

	Olaparib dose	Cediranib dose
CTCAE grade 3-4 ANC <1.0 G/L or Platelet count <50 G/L	Dose interruption until recovered to CTCAE Grade ≤1 for a maximum of 3 weeks. Upon recovery, olaparib dose should be reduced by one dose level. If repeat CTCAE Grade 3-4 occurrence, further dose reduce one or both IPs	Dose interruption until recovered to CTCAE Grade ≤1 for a maximum of 3 weeks. Upon recovery, cediranib dose should be reduced by one dose level. If repeat CTCAE Grade 3-4 occurrence, further dose reduce one or both IPs

Abbreviations: ANC absolute neutrophil count; CTCAE common terminology criteria for adverse events; IP investigational product

6.8.1.1 Use of hematopoietic agents

Use erythropoietin-stimulating agents per standard of care National Comprehensive Cancer Network (NCCN) and/or institutional guidelines, iron supplements, and/or transfusions as clinically indicated for management of anemia. Prescribing information for the erythropoiesis stimulating agents (including Aranesp, Epogen and Procrit) highlight that there is a potential risk of shortening the time to tumor progression or disease-free survival. Primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) is not recommended (Mountzios et al 2016). They do not alleviate fatigue or increase energy. They should not be used in patients with uncontrolled hypertension. The package inserts should be consulted.

If a patient develops febrile neutropenia, IPs should be stopped and appropriate management including G-CSF should be given according to local hospital guidelines. Please note that G-CSF should not be used within at least 24 hours of the last dose of olaparib unless absolutely necessary.

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

6.8.1.2 Dose modifications for hematologic toxicity

Patients who have IPs held for hematologic toxicities should have blood counts and differentials checked at least weekly until recovery; these data should be recorded in eCRF as extra laboratory examinations. If counts do not improve to CTCAE Grade 1 or better despite drug cessation for 3 weeks, patients should be referred to a hematologist for further assessment. A bone marrow analysis should be considered per hematology assessment.

For AEs that are unrelated to the study drug, study drug may be withheld for up to 3 weeks at the discretion of the treating Investigator.

Management of anemia

Anemia is a common adverse drug reaction related to olaparib. Cediranib is not reported to increase the risk of anemia. Management of anemia is in accordance with Table 10:

Table 10 Management of anaemia

	Olaparib dose	Cediranib dose
Hb <10 but ≥8 g/dL	Give appropriate supportive treatment and investigate causality. Investigator judgement to continue olaparib or interrupt dose for a maximum of 3 weeks. If repeat Hb **<10 but ≥8** g/dL, dose interrupt until Hb ≥10 g/dL for maximum of 3 weeks and upon recovery dose reduce to **150 mg bd** as a first step and to **100 mg bd** as a second step	No change
Hb < 8 g/dL	Give appropriate supportive treatment and investigate causality. Interrupt olaparib until improved to Hb ≥10 g/dL. Upon recovery dose reduce olaparib to **150 mg bd**	No change

Abbreviations: bd twice daily; Hb hemoglobin

Common treatable causes of anemia (eg, iron, vitamin B12 or folate deficiencies and hypothyroidism) should be investigated and appropriately managed. In some cases, management of anemia may require blood transfusions. Any subsequently required dose interruptions, related to development of anemia, or coexistent with newly developed neutropenia, and/or thrombocytopenia, will require olaparib dose reductions to 150 mg twice daily as a first step and to 100 mg twice daily as a second step.

If Hb drops to < 8 g/dL despite the dose reduction or more than one blood transfusion is required to recover Hb levels with no alternative explanation for the anemia, olaparib should be permanently discontinued.

6.8.1.3 Management of prolonged hematological toxicities while on study treatment

If a patient develops prolonged hematological toxicity such as:

- ≥ 2 week interruption/delay in olaparib due to CTCAE Grade 3 or worse anemia and/or development of blood transfusion dependence
- ≥ 2 week interruption/delay in 1 or both IPs due to CTCAE Grade ≥3 neutropenia (ANC <1 x 10^9/L)
- ≥ 2 week interruption/delay in 1 or both IPs due to CTCAE Grade ≥3 thrombocytopenia and/or development of platelet transfusion dependence (Platelets <50 x 10^9/L)

Check weekly differential blood counts including reticulocytes and peripheral blood smear. If any blood parameters remain clinically abnormal after 3 weeks of dose interruption, the patient should be referred to hematologist for further investigations. Bone marrow analysis

and/or blood cytogenetic analysis should be considered at this stage according to standard hematological practice. Both IPs should be discontinued if blood counts do not recover to CTCAE Grade ≤1 within 3 weeks of dose interruption.

Development of a confirmed myelodysplastic syndrome (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. Olaparib treatment should be discontinued if patient's diagnosis of MDS and/or acute myeloid leukemia (AML) is confirmed.

6.8.2 Non-hematologic toxicity

Cediranib should be discontinued should any of the following AEs occur: GI perforation; arterial thromboembolic events; PRES (radiologically confirmed); severe or medically significant hemorrhage and severe persistent hypertension despite maximal anti-hypertensive treatment.

Dose modifications for other non-hematologic events on IPs should be managed according to Table 11.

Table 11 General Management of Non-Hematologic Toxicity

Observation	Action
AE resolves promptly with supportive care	Maintain dose level
Any ≥Grade 3 non-hematologic (excluding grade 3 fatigue or easily correctable asymptomatic grade 3 laboratory abnormalities)	Hold IP(s)[a] for up to 3 weeks until toxicity resolves to ≤ Grade 1.
	Treatment may be restarted at one dose level lower for the IP(s) causing the toxicity (see Table 7 and Table 8), at the treating investigator's discretion[b]. Reoccurrence of Grade 3 or 4 toxicity would require dose reduction of both IPs.
Any grade 2 non-hematologic AE or grade 3 fatigue related to cediranib or olaparib that persists despite maximal support.	Hold IP(s)[a] for up to 3 weeks until toxicity resolves to Grade ≥1. Treatment may be restarted at one dose level lower for the IP(s) causing the toxicity (see Table 7 and Table 8), at the treating investigator's discretion[b].
Grade 3 or 4 non-hematologic AE related to cediranib and olaparib combination that does not resolve to Grade 0-2 within 3 weeks despite maximum supportive care after treating patient at the lowest reduced dose level[c]	Discontinue IP(s)

a. At the discretion of the investigator, one IP may be held or dose modified or discontinued independently if the observed toxicity is attributed to only one of the drugs, while the patient continued to receive the second drug not associated with the observed toxicity. The time a given drug is held should not exceed 3 weeks.

b. Patients who are at the lowest reduced dose level may have their drug resumed at that dose level after discussion with the AstraZeneca Study Physician and the Principal Investigator if evidence of clinical benefit.
c. For venous thromboembolic events, treatment may be resumed at the discretion of the investigator once patient is asymptomatic (Section 6.7.3.11).

Abbreviations: AE adverse event; IP investigational product(s)

6.8.3 Management of cediranib-related toxicity

6.8.3.1 Hypertension

Only doses of cediranib will be modified for hypertension; olaparib doses will not be reduced unless other toxicities are experienced.

In clinical trials, increases in BP have been reported within a few hours of starting cediranib. Since rapid changes in blood pressure can occur with cediranib treatment, with the potential for life-threatening complications if hypertension is not appropriately managed, all patients should check their BP twice daily for at least the first 8 weeks after starting cediranib, or, if antihypertensive management is required, until a stable anti-hypertensive regimen has been established, even if this requires more than 8 weeks. After 8 weeks or once a stable regimen has been achieved, BP monitoring may be reduced to once daily. Twice daily monitoring should be re-implemented after any cediranib dose interruption for 2 weeks or until the patient is re-established on a stable antihypertensive regimen, whichever takes longer.

Patient BP will also be measured during routine study visits: weekly during the first 4 weeks, every 2 weeks during the next 4 weeks and every 4 weeks thereafter, to ensure that BP guidelines are being correctly followed. Increase in BP should be treated promptly with standard antihypertensive therapy, ensuring that the maximum recommended dose and number of antihypertensive medicinal products is reached before considering cediranib dose adjustment. See Appendix G for suggested antihypertensive medications by class. Patients may have up to 4 drugs for management of hypertension prior to any dose reduction in cediranib.

If patients require a delay of > 3 weeks for management of hypertension, discontinuation of cediranib or protocol therapy may be considered after discussion with the PI and the AstraZeneca study physician. In case of persistent or severe hypertension, despite the optimal use of antihypertensive medicinal products and cediranib dose reduction, cediranib should be permanently discontinued.

Patients already taking antihypertensive therapy at baseline or those aged 75 years or older are at a higher risk of having elevated BP or may require more than one medicinal product or more intensive therapy. Pre-existing cardiovascular risks should be assessed and managed, and pre-existing hypertension should be adequately controlled before starting treatment with cediranib. Note: Stopping or reducing the dose of cediranib is expected to cause a decrease in BP. The treating physician should monitor the patient for hypotension and adjust the number and dose of antihypertensive medications accordingly.

Hypertension should be graded using the NCI CTCAE version 4.03. Please note: patients may have baseline hypertension meeting CTCAE grading criteria on study entry provided this is adequately controlled on maximum of 3 antihypertensive medications (see Section 3.1).

Baseline grade of hypertension should also be recorded in Medical History eForm.

Should patients require increase in dosing of BP medication or increased number of medications, they should then be noted to have hypertension related to study drug, with grading as per CTCAE version 4.03 criteria.

Table 12 provides hypertension monitoring and management guidance.

Table 12 Hypertension Monitoring and Management

Event	Antihypertensive Therapy	Blood Pressure Monitoring	Cediranib Dose Modification
Asymptomatic transient (<24 hours) increase by >20 mmHg diastolic or to >140/90 mmHg if previously within normal limits	Consider early initiation of BP medication for BP > 140/90 mmHg that is confirmed on a second reading. Cediranib can cause rapid escalation in BP, and early initiation of BP management can reduce likelihood of hypertension-related complications	Continue standard BP monitoring according to local practice and confirm resolution of BP to <140/90 mmHg within 24 hours.	None

Table 12 Hypertension Monitoring and Management

	Event	Antihypertensive Therapy	Blood Pressure Monitoring	Cediranib Dose Modification
	Recurrent or persistent (>24 hours) or symptomatic increase by >20 mmHg (diastolic) or to > 140/90 mmHg if previously within normal limits. Monotherapy may be indicated	Initiate BP medication for first line treatment. Suggestions: ACE inhibitor or Calcium Channel Blocker Escalate dose of medication in step wise fashion until BP is controlled or at a maximum dose If BP is not controlled to <140/90 mmHg with one "maximized" drug regimen, then add a second agent. Study drug does not need to be held unless otherwise clinically necessary Consider renal consult	Increase frequency of monitoring until stabilized to BP <140/90 mmHg	Do not withhold cediranib unless otherwise clinically necessary

Table 12 Hypertension Monitoring and Management

	Event	Antihypertensive Therapy	Blood Pressure Monitoring	Cediranib Dose Modification
	Requiring more than one drug or more intensive therapy than previously.	Maximize 2 drug regimen Suggestions: ACE-inhibitor + Calcium Channel Blocker Escalate doses of existing medication until BP is controlled or at a maximum dose. If BP is not controlled to <140/90 mmHg with two drug regimen, then add a third agent. Study Drug will not be held during trial of two drug combinations. Additional antihypertensive drugs, up to a total of 4, may be maximized for BP control. Consider consult with a BP management specialist if greater than 3 drugs are required for BP control.	Increase frequency of monitoring until stabilized to BP <140/90 mmHg	Do not withhold cediranib unless BP is not decreased to less than 150/100 mmHg 48 hours after multi-drug therapy is instituted or if clinical symptoms worsen (eg, headache). If BP is not controlled to less than 150/100 mmHg with maximal therapy or if clinical symptoms worsen, then withhold cediranib (up to 3 weeks) until maximum effect of the antihypertensive agents is achieved. If BP is reduced to Grade 1 within 3 weeks, cediranib may be resumed at prior dose.

Table 12 Hypertension Monitoring and Management

	Event	Antihypertensive Therapy	Blood Pressure Monitoring	Cediranib Dose Modification
	If threatening consequences OR SBP ≥180mmHg OR DBP ≥110mmHg	Initiate treatment Hospitalize patient for ICU management, IV therapy as necessary. 14 days are allowed to maximize the full effect of anti-hypertensive agents.	Intensive BP monitoring (hospitalization if necessary)	Withhold cediranib. If BP is reduced to Grade 1 within 3 weeks, cediranib may be resumed at a reduced dose after discussion with the AstraZeneca Study Physician and the Principal Investigator.

Abbreviations: ACE Angiotensin Converting Enzyme; BP blood pressure; DBP diastolic blood pressure; ICU intensive care unit; IV intravenous; SBP systolic blood pressure.

6.8.3.2 Diarrhea

Diarrhea is often observed with cediranib. Diarrhea usually starts early (within the first 4 weeks of treatment), however, it can occur at any time during treatment. Management of diarrhea should start at the first sign of diarrhea. Loperamide and advice on how to manage diarrhea should be readily available to patients from the start of cediranib treatment so that they can be applied at first episode of diarrhea. Active and early management of diarrhea is recommended even with Grade 1 diarrhea. Management is as shown in Table 13:

Table 13 Management of Diarrhea

Toxicity	Management/Modifications
Initial grade 1 or 2 diarrhea	Patients should start loperamide (per standard practice) and continue to take loperamide until patients are free from diarrhea for at least 12 hours. The dose of loperamide should not exceed 16 mg in a 24-hour period. Patients should also be counselled to start a BRAT diet. If diarrhea persists despite 24 hours of loperamide treatment, withhold cediranib for a maximum of 7 days, continue loperamide, and maintain hydration. Cediranib may be restarted at the same dose once patients have been free from diarrhea for 12 hours. Patients should be instructed to contact their study physician if mild or moderate (NCI CTCAE Grade 1 or 2) diarrhea persists for over 48 hours despite treatment with loperamide and cediranib dose interruption.

Table 13 Management of Diarrhea

Toxicity	Management/Modifications
For either persistent grade 2 diarrhea or grade 3 or 4 diarrhea	Patients with persistent or severe diarrhea (NCI CTCAE Grade 3 or higher) may also require dose reduction or discontinuation of therapy with cediranib, follow guidance in Table 7

Abbreviations: BRAT bananas, rice, applesauce, toast; CTCAE Common Terminology Criteria for Adverse Event; NCI National Cancer Institute.

6.8.3.3 Fatigue

Fatigue is a common adverse drug reaction reported for both cediranib and olaparib. Fatigue experienced by patients taking cediranib may be rapid in onset. During clinic visits, patients fatigue levels should be discussed. Patients should seek medical advice early if Grade 2 fatigue develops (moderate fatigue causing difficulty performing some activities of daily living).

Care should be taken to ensure that the nutritional status of the patients is optimized and patients should be encouraged to drink plenty of fluids. Patients should be encouraged to manage fatigue by alternating periods of rest with light aerobic exercise, which may improve the symptoms in some cases.

Consideration should be given to other possible causes of fatigue (eg, thyroid function, depression/insomnia and other concomitant medicinal products). Additionally, short interruption of cediranib dosing (initially 2-3 days-or longer-up to a maximum of 21 days) may help relieve fatigue. When symptoms improve cediranib should be restarted with the same dose or, if necessary, a dose reduction can be considered.

6.8.3.4 Proteinuria

Proteinuria is a common adverse reaction reported for cediranib and if this occurs during treatment, it should be managed according to Table 14. For management of suspected cases of nephrotic syndrome, refer Section 5.2.1.4.

Table 14 Management of Proteinuria

Proteinuria Value if following by urinalysis	Monitoring	Dose modification
Greater than 2+ AND Creatinine ≤1.5x ULN	Perform UPC	Continue study drugs at planned dose
Greater than 2+ AND Creatinine >1.5x ULN	Perform UPC	Interrupt cediranib until results of UPC are known (see below)
Based on results of the UPC[a]		
UPC ≤ 1.0	Continue monitoring according to Schedule of Assessments (Table 5)	Continue study drugs at planned dose
UPC > 1.0 and ≤3.5 AND Creatinine ≤1.5x ULN	Perform UPC at each routine visit	Continue study drugs at planned dose
UPC > 3.5 OR Creatinine >1.5x ULN	Perform UPC at each routine visit	Interrupt cediranib for up to 21 days and repeat UPC and creatinine assessment. If UPC resolves to <3.5 and creatinine to ≤1.5x ULN, resume cediranib with reduction in cediranib by one dose level. Consider consultation with nephrologist

[a] If UPC is <1.0 and creatinine >1.5x ULN, AE management should be followed as described above
Abbreviations: ULN upper limit of normal; UPC urine protein:creatinine ratio

6.8.3.5 Management of Thyroid Toxicities

The use of cediranib has been associated with elevations of TSH and patients should be managed as per Table 15. In all cases, IPs should continue unless clinically contraindicated. Referral to an endocrinologist should also be considered if thyroid abnormalities occur.

Table 15 Monitoring and Management of Thyroid Toxicities

Result of TSH and FT4	Action
Increases of TSH with normal FT4	Monitor
Increases in TSH with normal FT4 and adverse events suggestive of incipient hypothyroidism	Consider replacement thyroxine
Increase in TSH with reductions in FT4	Consider replacement thyroxine

Abbreviations: FT4 free thyroxine; TSH thyroid stimulating hormone

6.8.3.6 Decrease in LVEF

Patients who have any of the following should undergo an echocardiogram (ECHO) or multigated acquisition (MUGA) scan at baseline and as clinically indicated (see Table 5) while on study:

- Prior treatment with anthracyclines
- Prior treatment with trastuzumab
- Prior central thoracic RT, including RT to the heart
- History of myocardial infarction within 6 to 12 months or history of other significant impaired cardiac function (Patients with history of myocardial infarction within 6 months are excluded from the study)

The decision to continue or interrupt cediranib/olaparib is based on the LVEF as it relates to the institution's LLN and change in ejection fraction from screening (LVEF as measured at enrollment) according to Table 16.

Table 16 Monitoring and Management of Decreased LVEF

Relationship of LVEF to Institution's LLN at baseline	LVEF Decrease <10%	LVEF Decrease 10-15%	LVEF Decrease >15%
Normal	Continue	Continue	Continue and repeat MUGA/ECHO within 4-8 weeks
1-5% below LLN	Continue and repeat MUGA/ECHO within 4-8 weeks	Continue and repeat MUGA/ECHO within 4-8 weeks	Interrupt cediranib and repeat MUGA/ECHO within 3 weeks
> 6% below LLN	Continue and repeat MUGA/ECHO within 4-8 weeks	Interrupt cediranib and repeat MUGA/ECHO within 3 weeks	Interrupt cediranib and repeat MUGA/ECHO within 3 weeks

Abbreviations: ECHO echocardiogram; LLN lower limit of normal; LVEF left ventricular ejection fraction; MUGA multigated acquisition.
LVEF decreases in percentage points.

6.8.3.7 Posterior Reversible Encephalopathy Syndrome (PRES)

Posterior reversible encephalopathy syndrome (PRES) has been uncommonly reported in clinical studies with cediranib. PRES is a neurological disorder which can present with headache, seizure, lethargy, confusion, blindness and other visual and neurologic disturbances, and can be fatal. Mild to severe hypertension may be present. In patients developing PRES, treatment of specific symptoms including control of BP is recommended. Confirmation of PRES requires brain imaging, preferably MRI. Cediranib should be discontinued following confirmation of PRES. The safety of reinitiating cediranib in patients previously experiencing PRES is not known.

6.8.3.8 Gastrointestinal perforation

GI perforation has been uncommonly reported in cediranib treated patients and may be fatal. Cediranib should be used with caution in patients at risk and permanently discontinued in patients who develop GI perforation.

6.8.3.9 Fistula

In patients treated with cediranib, fistula has been reported and reflected the location of the underling malignancy. In the ovarian cancer population, vaginal fistula has been uncommonly reported in cediranib treated patients. Cediranib should be used with caution in patients at risk of fistula and discontinuation of cediranib should be considered in patients who develop fistulae.

6.8.3.10 Arterial thromboembolism

Arterial thromboembolic events (including transient ischemic attack and ischemic stroke) have been reported in clinical studies with cediranib. Cediranib should be used with caution

in patients who are at an increased risk of thrombotic events or who have a history of thrombotic events. Cediranib should be permanently discontinued in patients who develop an arterial thromboembolic event.

6.8.3.11 Venous thromboembolism

Venous thromboembolic events including pulmonary embolism and deep vein thrombosis have been commonly reported in patients treated with cediranib. Anticoagulant treatment should be started in accordance with clinical practice. Discontinuation of cediranib may be considered. Cediranib should be used with caution in patients at risk of venous thromboembolism.

6.8.3.12 Wound healing

Treatment with cediranib should be stopped at least 2 weeks prior to scheduled surgery. The decision to resume cediranib therapy after surgery should be based on clinical judgment of adequate wound healing. In patients who experience wound healing complications during therapy, treatment with cediranib should be interrupted until the wound is fully healed. No formal studies of the effect of cediranib on wound healing have been conducted; however, in the ICON6 pivotal study there was no evidence of an increase in wound healing complications in cediranib treated patients compared with placebo.

6.8.3.13 Elderly

There is a limited amount of safety data available for cediranib use in patients aged 75 years and older. Based on a population PK analysis, the clearance of cediranib decreased with age, however, no dose adjustment is needed given the small impact on exposure or variability. Caution should be taken when treating patients who are aged 75 years or older with cediranib. In case of toxicity dose pause or dose reduction may be considered.

6.8.3.14 Mild/moderate renally impaired patients

Patients with mild and moderate renal impairment discontinued cediranib more often due to adverse events, particularly when cediranib was co-administered with chemotherapy. Population PK analysis showed that no adjustment of cediranib dose is required in this population as cediranib is minimally renally cleared; however, cediranib clearance may be decreased in patients with low body weight. In the ICON6 pivotal study, patients with mild or moderate impairment had lower median body weight compared with patients with normal renal function. Caution should be exercised in patients with mild and moderate renal impairment and a cediranib dose adjustment should be considered in case of signs of toxicity.

For information on use of olaparib in renally-impaired patients, please see Section 6.8.4.4

6.8.3.15 Weight decreased

In the ICON6 study, weight decreased was very commonly reported in cediranib treated patients. Weight loss (≥7%) in cediranib-treated patients was associated with higher incidence of decreased appetite, vomiting and stomatitis, although these events were also commonly reported in patients who did not lose weight.

6.8.4 Management of olaparib associated toxicity

6.8.4.1 Management of MDS/AML

Patients who develop MDS/AML on treatment should be discontinued from olaparib treatment and managed appropriately.

6.8.4.2 Management of olparib-related new or worsening pulmonary symptoms

If new or worsening pulmonary symptoms (eg, dyspnea) or radiological abnormalities occur in the absence of a clear diagnosis, an interruption in 1 or both IPs dosing is recommended and further diagnostic workup (including a HRCT scan) should be performed to exclude pneumonitis.

Following investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, then IP(s) can be restarted, if deemed appropriate by the investigator. If significant pulmonary abnormalities are identified, these need to be discussed with the Study Physician.

6.8.4.3 Management of nausea and vomiting

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.

No routine prophylactic anti-emetic treatment is required at the start of treatment with the IPs, however, 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. Taking olaparib tablets with food may help alleviate symptoms of nausea and vomiting.

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

6.8.4.4 Management of renal impairment

If subsequent to study entry and while still on study treatments, a patient's estimated creatinine clearance (CrCL) falls below the threshold for study inclusion (<50 mL/min), retesting should be performed promptly. A dose reduction of olaparib is recommended for patients who develop moderate renal impairment (calculated CrCL by Cockcroft-Gault equation of ≥31 mL/min and ≤50 mL/min) for any reason during the course of the study: the dose of olaparib should be reduced to 150 mg bd.

Because the CrCL determination is only an estimate of renal function, in instances where the CrCL falls to between 31 mL/minutes and 50 mL/minutes, the Investigator should use his or her discretion in determining whether a dose change or discontinuation of therapy is warranted.

Olaparib has not been studied in patients with severe renal impairment (CrCL ≤30 mL/minutes) or end-stage renal disease; if patients develop severe impairment or end stage disease is it recommended that olaparib be discontinued. For information on use of cediranib in renally-impaired patients, please see Section 6.8.3.14.

6.8.5 Interruptions for intercurrent non-toxicity related events

IP(s) dose interruption for conditions other than toxicity resolution should be kept as short as possible. If a patient cannot restart IP(s) within 3 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.

Both IPs should be stopped at least 2 weeks prior to planned surgery. After surgery both IPs can be restarted when the wound has healed. No stoppage of IPs is required for any needle biopsy procedure.

Both IPs should be discontinued for a minimum of 3 days before a patient undergoes radiation treatment. Both IPs should be restarted within 3 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.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product(s)

Table 17 Identity of investigational product(s)

Investigational product[a]	Dosage form and strength	Manufacturer
Olaparib	150 mg and 100 mg tablet	Abbvie on behalf of AstraZeneca
Cediranib	20 mg and 15 mg tablet	AstraZeneca

a Descriptive information for olaparib and cediranib can be found in the respective olaparib and cediranib Investigator's Brochures

7.1.1 Cediranib

Cediranib is available as a beige film-coated tablet containing 20 mg or 15 mg of cediranib. Patients will be administered cediranib study treatment tablets orally at a dose of 30 mg od. The planned dose of 30 mg od will be made up of 2 × 15 mg tablets od. One x 20 mg and 1 x 15 mg tablets will be used to manage dose reductions.

The dose of cediranib can be taken at the same time as the morning dose of olaparib and can be taken with or without food, in a similar way each morning.

7.1.2 Olaparib

Olaparib is available as a green film-coated tablet containing 150 mg or 100 mg of olaparib. Patients will be administered olaparib study treatment tablets orally at a dose of 200 mg bd. The planned dose of 200 mg bd will be made up of 2 × 100 mg tablets bd. One x 150 mg and 1 x 100 mg tablets will be used to manage dose reductions.

The olaparib tablets should be swallowed whole and not chewed, crushed, dissolved or divided. Olaparib tablets can be taken with or without food.

7.2 Dose and treatment regimens

Dose reductions for toxicity are permitted for either or both IPs (see Section 6.7).

7.2.1 Cediranib

For all centers, cediranib will be packed in high-density polyethylene bottles with child-resistant closures. The cediranib study treatment will be dispensed to patients. Multiple bottles of study treatment may be required for dispensing in order to make up the desired dose.

Patients will be administered cediranib study treatment tablets orally at a dose of 30 mg od. The planned dose of 30 mg od will be made up of 2 × 15 mg tablets od. One x 20 mg and 1 x 15 mg tablets will be used to manage dose reductions.

Doses of study treatment should be taken at the same time each morning. The dose of cediranib can be taken at the same time as the morning dose of olaparib and can be taken with or without food, in a similar way each morning. For patients with difficulty swallowing tablets, cediranib tablets may be dispersed in non-carbonated drinking water.

If a patient misses a dose, the patient should be advised to take the dose as soon as possible provided this happens within 6 hours of the scheduled time. If it is more than 6 hours after the scheduled time, cediranib should not be taken for that day. Cediranib should be taken as scheduled on the next day. A patient should not take more than a single daily dose on a given day.

7.2.2 Olaparib

For all centers, olaparib will be packed in high-density polyethylene bottles with child-resistant closures. The olaparib study treatment will be dispensed to patients. Multiple bottles of study treatment may be required for dispensing in order to make up the desired dose.

Patients will be administered olaparib study treatment tablets orally at a dose of 200 mg bd. The planned dose of 200 mg bd will be made up of 2 × 100 mg tablets bd. One x 150 mg and 1 x 100 mg tablets will be used to manage dose reductions.

Doses of study treatment should be taken at the same time each day approximately 12 hours apart. All doses should be taken with approximately 240 mL of water. The olaparib treatment tablets should be swallowed whole and not chewed, crushed, dissolved or divided. Olaparib tablets can be taken with or without food.

If vomiting occurs shortly after the study treatment 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.

7.3 Labelling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language.

Specific dosing instructions will not be included on the label; the site must complete the "Patient Dispensing Card" with the details of the dosing instructions at the time of dispensing. The patient emergency contact details will not be on the label, but can be found in the informed consent and the 'Patient Dispensing Card'. For emergency purposes, the patient must be in possession of the emergency contact details at all times.

7.4 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. The IP labels on the bottles specify the appropriate storage.

7.5 Compliance

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

Treatment compliance will be assured by reconciliation of site drug accountability logs. Patients should be given clear instructions on how and when to take their IPs. Patients will self-administer olaparib and cediranib. 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 olaparib and cediranib at the appropriate scheduled visit, when a new bottle will be dispensed. Patients will be instructed to record dates of missed or held doses using a handheld electronic device (the same device used for collection of PRO data; see Section 5.3.1). These data will be reviewed by the Investigator at each patient visit and data entered in eCRF by the site staff. 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 study protocol.

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

Study site personnel, will account for all study drugs received at the site, unused study drugs and for appropriate destruction. Certificates of delivery, destruction and return (as applicable for particular study drug) should be signed.

7.7 Concomitant and other treatments

The Investigator must be informed as soon as possible about any medication taken from the time of screening until the end of the study treatment period (treatment discontinuation or FPV visit). Any concomitant medication(s), including herbal preparations, taken during the study will be recorded in the eCRF.

Medications that should NOT be administered

No other anti-cancer therapy (chemotherapy, immunotherapy, hormonal therapy (Hormone replacement therapy (HRT) is acceptable), RT, biological therapy or other novel agent) is to be permitted while the patient is receiving one or both IPs.

Live virus and bacterial vaccines should not be administered whilst the patient is receiving one or both IPs 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 the combination of cediranib and olaparib are unknown.

The use of any natural/herbal products or other “folk 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.

Cediranib and inducers of PgP/UGT

In vitro data indicate that cediranib is unlikely to cause interactions with CYP450 inducers, inhibitors, and substrates. Cediranib oxidative metabolism appears to be mediated by flavin-containing monooxygenase enzymes FMO1 and FMO3 and glucuronidation by UGT1A4. Co-administration of cediranib with strong inducers of PgP/UGT decrease cediranib plasma concentrations; therefore, use of potent inducers of UGT/PgP (eg, rifampicin, carbamazepine, phenobarbital, phenytoin and St. John Wort) should be avoided if possible. Cediranib is a substrate of MDR1 (Pgp), and possible substrate of breast cancer resistant protein (BCRP). Cediranib is not an inhibitor of OAT1 and OAT3, but it has a low potential to inhibit MDR1 (Pgp), BCRP, OATP1B1, OATP1B3, OCT2, MATE1. The clinical impact of this finding is unknown. Cediranib may act as an inhibitor of renal tubular MATE2-K, this could increase exposure of co-administered agents such metformin or to endogenous agents such as creatinine; however, the ICON6 study showed that increases of blood creatinine caused by 20 mg/day cediranib treatment were infrequent (4.4%) and only mild in severity, suggesting the clinical impact of renal tubular MATE2-K inhibition by cediranib is small.

Olaparib and CYP 3A4/5 enzymes

CYP3A4/5 are the isozymes predominantly responsible for the metabolic clearance of olaparib. Clinical studies to evaluate the impact of known CYP3A inhibitors and inducers have shown that co-administration of a strong CYP3A inhibitor increased olaparib maximum plasma concentration (C_{max}) 1.42-fold (90% CI: 1.33-1.52) and increased mean area under the plasma drug concentration-time curve (AUC) 2.70-fold (90% CI: 2.44-2.97); co-administration of a strong CYP inducer decreased C_{max} by 71% (treatment ratio: 0.29; 90% CI: 0.24-0.33) and mean AUC by 87% (treatment ratio: 0.13; 90% CI: 0.11-0.16).

Consequently, to ensure patient safety, the following potent inhibitors of CYP3A4/5 must not be used during this study for any patient receiving olaparib (eg, itraconazole, telithromycin, clarithromycin, boosted protease inhibitors, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate inhibitors (ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil) of this isozyme should not be taken with the IPs in this study.

Strong CYP 3A4/5 inducers (eg, phenobarbital, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine, enzalutamide and St John's Wort) and moderate inducers CYP 3A4 inducers (eg, bosentan, efavirenz, modafinil) should not be taken with the IPs in this study.

After enrollment if the use of any potent inducers or inhibitors of CYP3A4/5 are considered necessary for the patient's safety and welfare, the investigator must contact the AstraZeneca Study Physician. A decision to allow the patient to continue in the study will be made on a case-by-case basis.

Effect of olaparib on other drugs

- CYP3A4 substrates: hormonal contraceptive, simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and quetiapine
- CYP2B6 substrates: bupropion, efavirenz
- OATP1B1 substrates: bosentan, glibenclamide, repaglinide, statins and valsartan
- OCT1, MATE1 and MATE2K substrates: metformin
- OCT2 substrates: serum creatinine
- OAT3 substrates: furosemide, methotrexate

Based on limited in vitro data, olaparib may increase the exposure to substrates of CYP3A4, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K. Based on limited in vitro data, olaparib may reduce the exposure to substrates of 2B6. Caution should be observed if substrates of these isoenzymes or transporter proteins are co-administered.

Anticoagulant Therapy

Patients who are taking warfarin may participate in this trial; however, it is recommended that prothrombin time (International Normalized Ratio [INR] and activated partial thromboplastin time) be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Subcutaneous heparin and low molecular weight heparin are permitted.

Anti-emetics/Anti-diarrheal

From screening onwards, should a patient develop nausea, vomiting and / or diarrhea, then these symptoms should be reported as AEs (see Section 6.3) and appropriate treatment of the event given.

Palliative radiotherapy

Palliative RT 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. Both IPs should be discontinued for a minimum of 3 days before a patient undergoes therapeutic palliative radiation treatment. Both IPs 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 one or both IPs. Patients may continue the use of bisphosphonates or denosumab for bone disease and corticosteroids for the symptomatic control of brain metastases provided the dose is stable before and during the study and they were started at least 4 weeks prior to the first doses of IPs.

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 until the end of the study.

Other concomitant treatment

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

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

7.8 Post Study Access to Study Treatment

There are no plans to provide olaparib and/or cediranib to the patients after discontinuation of the IPs. After discontinuation of IPs, the investigator will be at liberty to define further most appropriate anti-cancer treatment. Information on subsequent PARP and VEGF inhibitors and other anti-cancer therapies should be recorded on the clinical database as part of survival follow-up.

8. STATISTICAL ANALYSES BY ASTRAZENECA

8.1 Statistical considerations

A comprehensive Statistical Analysis Plan (SAP) will be prepared prior to first patient enrolled and any subsequent amendments will be documented, with final amendments completed prior to database lock. Additional details relating to the ICR will be detailed in the ICR Charter.

An interim futility analysis will take place after 20 evaluable (by Investigator assessment) patients have received at least 1 dose of IP and have been followed for at least 4 months. Patients in the futility analysis will also have their baseline scans reviewed by ICR to evaluate the concordance rate on measurable disease at this stage. Enrollment will continue during the futility analysis. Assuming the study passes the futility assessment, the data cut-off for the primary analysis of ORR will take place 8 months after the last patient has received her first dose of IP, to allow opportunity for all patients to complete at least 4 RECIST follow-up assessments. Patients will be followed for survival and analysis of OS will also take place at this time. Patients should be contacted or other data sources checked (see Section 3.10.2) in the 2 weeks following the data cut-off for the primary analysis to provide current survival data. At this time, the CSR will be written including the analysis of the confirmed ORR by ICR using RECIST 1.1 criteria, supported by Investigator assessment of ORR and by other efficacy endpoints (DoR, DCR, PFS, OS and TDT), PROs and safety/tolerability variables.

Following the data cut-off for the primary analysis, no further statistical analysis of the data will be conducted.

8.2 Sample size estimate

The study originally planned to recruit 100 patients over approximately 12 months. The primary analysis scheduled at 8 months after the last patient received her first dose of IP (approximately 20 months after study start), allows all patients to have at least 4 RECIST follow-up assessments.

An interim futility analysis of ORR (confirmed and/or unconfirmed CRs and PRs based on investigator assessment) will take place after 20 evaluable patients (ie, with measurable disease (by Investigator assessment) have received at least 1 dose of IP and have been followed for at least 4 months. If less than 4 of the 20 have responded the study may be stopped for futility. If 4 or more patients have responded the study will continue to the primary analysis.

The study design was formulated within a Bayesian framework (Fisch et al 2015) based on dual criteria to show improvement over the expected response rate under current standard treatments (20% RR targeted as an improvement over <15% RR based on chemotherapy, Davis et al 2014) and to have a RR of a relevant size (approximately 30%, similar to the RR seen for bevacizumab plus chemotherapy in the AURELIA trial, Pujade-Lauraine et al 2014) defined as follows:

1. to have high confidence (>90%) that the true ORR is at least 20% or probability (ORR≥ 20%) >0.9 and

2. an observed rate of 30/100 is seen at the primary analysis.

The futility rule above (stop if number of responses is <4), was chosen so that the trial may stop if there is a low chance (<10% predictive probability) of 30 or more responses being observed at the primary analysis. Computation of posterior and predictive probabilities used a neutral prior ie, beta (1/3, 1/3) distribution (Kerman 2011), for the ORR. The predictive probability of observing a given number of responses at the end of the trial given the observed responses at the interim analysis is computed using a beta binomial distribution.

With 30 responders out of 100 at the primary analysis we would be >99% confident that the ORR is greater or equal to 20% and 94.6% confident that the ORR is ≥23%. It is noted that the interim analysis is based on unconfirmed, investigator assessed RECIST data, whereas the primary analysis will be based on ICR assessed data with responses confirmed at least 4 weeks after the initial response. Data from the OCEANS study indicated an approximate 1.5% reduction in response by ICR compared with investigator response (Aghajanian et al 2014). If only 26 patients out of 100 were to meet the latter definition of response at the primary analysis there would still be >90% confidence that the true rate was greater than or equal to 20%.

Assuming median PFS of 6 months, 73% PFS events are expected at the primary analysis at 8 months after the last patient receives her first dose of IP. The original analysis for OS at 12 months after last patient receives her first dose of IP would expect 59% deaths.

The study now plans to recruit approximately 60 patients and analysis of OS, originally planned at 12 months after the last patient received her first dose of IP, will now occur at 8 months after the last patient received her first dose of IP. Based on the revised duration of recruitment and assuming a median PFS of 6 months as originally planned and a median of 12 months for OS, 80% PFS events and 57% OS events are expected to occur at the time of the analysis.

Table 18 presents the 95% CIs for some possible response rates which give an indication of the precision of the response rate that might be seen.

Table 18 Response rates and associated 95% CIs for a sample of 60

Response (n)	Response (%)	95% CI
5	8.3%	(1.3%, 15.3%)
10	16.7%	(7.2%, 26.1%)
15	25.0%	(14.0%, 36.0%)

CI confidence interval

8.3 Definitions of analysis sets

8.3.1 Full analysis set (FAS)

All patients who received at least one dose of either IP will be included in the full analysis set.

8.3.2 Efficacy analysis set (EFR population)

The EFR analysis set will be all patients who have received at least one dose of either IP and have measurable disease at baseline according to the independent review of baseline imaging data.

The primary analysis of ORR, and analyses of DoR and DCR by ICR will be produced based on the EFR analysis set. All other efficacy variables (ORR, DoR, DCR based on investigator assessment; PFS, OS, TDT) and PRO variables will be summarized using the FAS.

Demographic data will be summarized for the FAS and to support the primary analysis, also for the EFR set (if different).

8.3.3 Safety analysis set

This is the same set as the FAS; ie, all patients who received at least one dose of either IP.

8.3.4 PK analysis set

All patients in the FAS providing at least 1 reportable PK concentration.

8.4 Outcome measures for analyses

Independent Central Review of RECIST based assessments

The ICR of all 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 ICR. Prior RT reports for patients (at baseline) and information on any lesions that were biopsied to provide a tumor sample for study entry (see Section 5.7.2) will also be provided to allow the selection of appropriate target lesions. The imaging scans will be reviewed by two independent radiologists using RECIST 1.1 criteria and will be adjudicated if required. For each patient, the ICR will define the overall visit response data (CR, PR, SD, PD or not evaluable [NE]) and the relevant scan dates for each time point (ie, for visits where response or progression is/is not identified). If a patient has had a tumor 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).

Further details of the ICR will be documented in the Independent Review Charter.

Investigator RECIST based assessments

From the investigators review of the imagining scans, the RECIST tumor response data will be used to determine each patient's visit response according to RECIST version 1.1. 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 tumor 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).

8.4.1 Primary Endpoint

Objective Response Rate (ORR)

ORR is defined as the number (%) of patients with measurable disease at baseline, with at least one visit response of CR or PR that is confirmed at least 4 weeks later. For the primary analysis ICR is required for both the initial response and confirmation. Data obtained up until progression, or last evaluable assessment in the absence of progression, will be included in the assessment of ORR. However, any CR or PR which occurred or was confirmed after a further anticancer therapy was received will not be included in numerator of the ORR calculation. In the case where a patient has two non-consecutive visit responses of PR or CR, then, as long as the time between the 2 visits of PR or CR is greater than 4 weeks and there is no PD between the PR visits, the patient will be defined as a responder. Note that CR followed by PR is classed as progression.

8.4.2 Secondary endpoints

Duration of response (DoR)

DoR will be defined as the time from the date of first documented response, (that is subsequently confirmed) until date of documented progression or death in the absence of disease progression. The date of the response start will be defined as the latest of the dates contributing towards the first visit response of PR or CR. If the response is not confirmed, it will not be included. The end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. If a patient does not progress following a response, then their duration of response will use the PFS censoring time.

Disease control rate (DCR)

DCR is defined as the percentage of patients who have a best overall response of CR or PR or SD (at 6 months).

Progression free survival (PFS)

PFS is defined as the time from date of first dose until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from study 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 three or more missed RECIST assessments 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.

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.

Overall visit assessments will be determined for each assessment (scheduled or unscheduled) and will contribute to the derivation of PFS. Objective disease progression is defined as: at least a 20% increase in the sum of the diameters of the target lesions (compared with a previous minimum sum) and an absolute increase of >5 mm, an overall assessment of progression or a new lesion.

Overall survival (OS)

OS is defined as the time from the date of first dose 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 the primary analysis, and if patients are confirmed to be alive (or if the death date is post the relevant data cut-off date) these patients will be censored in the associated analyses at the date of the data cut off.

Time to discontinuation of IPs or death (TDT)

TDT is defined as the time from the date of first doses of IPs to the earlier of the date of discontinuation of both IPs, or death date. Both IPs should be discontinued at the same time but in rare circumstances discontinuation of one of the IPs before the other may be allowed (see Section 3.9). In such a case, TDT will reflect the time from the date of first dose to the earliest IP discontinuation date.

HRQoL Analyses:

The EORTC-QLQ-C30 and EORTC-QLQ-OV28 questionnaires will be used. Descriptive statistics of absolute scores and change from baseline of all subscales will be presented and plots will be generated as appropriate to interpret changes over time.

Proportions of patients who had improved, stayed the same or deteriorated for all subscales (symptom and functioning scales) will be presented. A 10 point change in score will be used as cut-off point. The quantity and impact of missing data will be evaluated. If warranted, some investigation of HRQoL data by whether patients are still taking study drug will be performed.

- Symptom Improvement Rate at 8 weeks

– For dyspnea, pain and constipation from QLQ-C30 and abdominal/GI symptoms from QLQ-OV28, the symptom improvement rate at 8 weeks will be defined as the number (%) of patients showing a clinically meaningful improvement (a decrease from baseline score >10; Osoba et al 2005) in that symptom from baseline. The denominator will consist of a subset of the FAS population who have a baseline symptom score >10.

8.4.3 Other endpoints

Patient reporting of CTCAE symptoms

The PRO-CTCAE questionnaire will be used to derive patient reporting of CTCAE symptoms: nausea, vomiting, diarrhea, decreased appetite, fatigue, and dizziness.

Safety variables

Safety and tolerability will be assessed in terms of AEs, deaths, laboratory data, vital signs including BP and ECGs. Any AE occurring before the start of IP will not be included in the summary tables of AEs.

Any AE occurring within 30 days of discontinuation of IPs (ie, the last dose of cediranib + olaparib) or the last dose of the last IP to be discontinued, in the rare case where discontinuation dates are different will be included in the AE summaries.

Blood pressure data collected electronically (see Section 5.2.4.1) will not be reported in the CSR. Patient profiles and BP data over time for patients may be evaluated in an exploratory analysis at a later time.

8.5 Methods for statistical analyses

Descriptive statistics will be used for all variables, as appropriate. Continuous variables will be summarized by the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by frequency counts and percentages for each category. Unless otherwise stated, percentages will be calculated out of the FAS.

Baseline will be the last assessment of the variable under consideration prior to the intake of the first dose of IP.

8.5.1 Analysis of the primary variable ORR

The primary analysis will be based on ICR assessments of tumor response. Only patients with a confirmed CR or PR, by ICR, at least 4 weeks after the initial response will be counted as responders.

The number of responders (confirmed CR or PR) will be modelled using a binomial distribution with a neutral Beta (1/3,1/3) prior distribution on the rate.

The mean and median of the posterior distribution of ORR will be presented, along with the standard deviation and a 95% credible interval around the mean (based on the highest posterior density [Lee, 1997]). The observed ORR by ICR will also be presented with 95% exact (Clopper Pearson) CIs.

The posterior probabilities of the ORR being larger than 15%, 20% and 24% will be also computed. To further characterize the RR, the posterior probability of showing low (<15%), moderate (≥15%- <20%), high (≥20%- <24%) or substantial (≥24%) efficacy will be presented.

Summaries of the number of patients with best response in each of the follow categories will be presented: CR, PR, SD, PD and NE. For the interim analysis, the CR (PR) category will be split into confirmed CR (PR) and unconfirmed CR (PR).

At the time of primary analysis, ORR and exact 95% CI (Clopper Pearson) will be also be presented for the following:

- ORR by investigator assessment
- ORR for both confirmed and unconfirmed responses based on ICR assessment
- ORR based on ICR assessment in the subgroup of patients carrying a somatic deleterious or suspected deleterious variant in either of the *BRCA* genes (*BRCA1* or *BRCA2*) or in HRR-associated genes identified with current and potential future tumor based *BRCA* or HRR gene mutation assays (ICR and Investigator assessment)

The concordance between ORR (confirmed responses) as assessed by ICR and by Investigator will be presented.

8.5.2 Analysis of the secondary variable(s)

Disease Control Rate (DCR)

DCR is defined as confirmed CR, PR or SD for at least 6 months. DCR based on ICR in the evaluable for response analysis set will be presented together with 95% exact (Clopper Pearson) CIs. DCR will be presented based on the Investigator assessment as a sensitivity analysis.

Duration of response (DoR)

DoR in responding patients will be summarized and the number (%) of responding patients with a DoR >3, >6, >9 and >12 months will be presented. A Kaplan Meier plot and median DoR with 95% CI (calculated from the Kaplan-Meier plot) will be presented. DoR will be presented based on the ICR, and (as a sensitivity analysis) based on the Investigator assessment.

Progression free survival (PFS)

PFS will be displayed using a Kaplan Meier plot. The number of events, the type of event (RECIST 1.1 progression or death), median time to event (calculated from the Kaplan-Meier plot), and the proportion of patients without an event at 3, 6, 12 and 18 months will be summarized.

Overall survival (OS)

OS will be displayed using a Kaplan-Meier plot. The number of events, median time to event (calculated from the Kaplan-Meier plot), and the proportion of patients without an event at 3, 6, 12 and 18 months will be summarized.

Subsequent anticancer treatment

Subsequent anticancer treatment will be summarized descriptively at the primary analysis.

Time to discontinuation of study treatment or death (TDT)

TDT will be displayed using a Kaplan-Meier plot. The number of events, median time to event (calculated from the Kaplan-Meier plot), and the proportion of patients without an event at 3, 6, 12 and 18 months will be summarized.

HRQoL Assessments

HrQoL data will be presented using summaries and descriptive statistics, and will be detailed in the SAP.

Safety Assessments

Safety and tolerability data will be presented using summaries and descriptive statistics, and will be detailed in the SAP.

8.5.3 Subgroup analysis (if applicable)

The analyses of ORR, DCR, DoR, PFS and OS will be repeated for patients in and not in the following two subgroups:

- patients carrying a somatic deleterious or suspected deleterious variants in either of the *BRCA* genes (*BRCA1* or *BRCA2*) identified with current and potential future tumor based *BRCA* mutation assays
- patients identified as having a deleterious or suspected deleterious variants in HRR-associated genes identified with current and potential future HRR gene mutation assays.

Other subgroups may be analyzed, as detailed in the SAP.

8.5.4 Interim analysis

An interim futility analysis will take place after 20 evaluable (by Investigator assessment) patients have received IPs and have been followed for at least 4 months. The study may be stopped for futility if there are less than 4 responders (confirmed and/or unconfirmed responses) out of the first 20 patients in which case the predictive probability of observing 30 responders or more at the end of trial is ≤4.6%. Computation of posterior and predictive probabilities will use a neutral prior ie, beta (1/3, 1/3) distribution (Kerman 2011), for the ORR. The predictive probability of observing a given number of responses at the end of the trial given the observed responses at the interim analysis is computed using a beta binomial distribution.

8.5.5 Sensitivity analysis

ORR, DCR, DoR and PFS will be re-analyzed using the investigator assessment of tumor response instead of ICR assessment, as sensitivity analyses.

8.5.6 Exploratory analyses

The analyses of the exploratory endpoints will be further detailed in the SAP.

PRO-CTCAE

PRO-CTCAE data will be presented using summaries and descriptive statistics based on the FAS and further details will be provided in the SAP.

Biomarkers

The following biomarkers will be analyzed using plots and descriptive summary statistics.

- Biomarker of potential HRDs, including genomic scarring, *BRCA1* methylation, and other genes that might modify HRD.
- Biomarkers of gene expression signature for angioimmune/angio/immune/metabolic categorization
- Angiogenic biomarkers such as VEGF-A, C, D; sVEGFR2, Tie2, Ang1, 2; leptin; IL6

CA-125

Analysis of CA-125 samples 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 and the WBDC/and/or ePROs system(s) utilized.

The PI will ensure that appropriate training relevant to the study is given to all site 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 protocol, that data are being accurately and timely recorded in the eCRFs, 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 eCRFs 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 center needs information and advice about the study conduct. AstraZeneca medical personnel will be readily available to discuss study related medical questions or problems with the investigator(s). Contact details are provided separately in the Investigator Study File.

9.2.1 Source data

Refer to the CSA for location of source data.

9.2.2 Study agreements

The Principal Investigator at each center 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 (CSP) and the CSA, the terms of CSP 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

The end of the study is defined as 'the last visit of the last patient undergoing the study' (ie, LSLV) or when the Sponsor decides to discontinue the study. There will be a primary data cut-off defined at approximately 8 months (LSLV) after the last patient received her first dose

of study treatment. Data cut-off will be followed by clinical database lock when all data for all patients have been collected.

The study is expected to start in Quarter 3, 2016 and to end by Quarter 3, 2019.

The study may be terminated at individual centers if the study procedures are not being performed according to 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 either cediranib or olaparib.

An interim futility analysis will take place after 20 evaluable patients (ie, with measurable disease [by investigator assessment] and received at least one dose of IP) have been recruited and followed for at least 4 months. Assuming the study passes the futility assessment, the data cut-off for the primary analysis of ORR and OS for the full CSR will take place 8 months after the last patient received her first dose of IP, to allow opportunity for all patients to complete 4 RECIST follow-up assessments and to allow responding patients to have a DoR greater than 6 months. At this time, the clinical study database will close to new data and all efficacy, HRQoL and safety/tolerability information will be summarized for preparation of the CSR. Patients are permitted to continue to receive IPs beyond the FPV if, in the opinion of the Investigator, they are continuing to receive benefit from treatment with cediranib and/or olaparib and have not met any discontinuation criteria. Such patients will complete a FPV, which will occur at their last scheduled visit prior to data cut-off. For further information regarding the FPV please refer to Section 4.4. For patients who continue to receive treatment beyond the FPV, Investigators will assume a manual drug ordering process for IPs.

Patients who continue to receive treatment beyond the FPV are to be followed in accordance with the Medical Standard of Care and as deemed appropriate by the Investigators. Serious adverse event reporting (on paper) will continue to ensure safety data collection and monitoring of the patients while receiving the investigational product. It is recommended that Investigators continue to observe ongoing patients at the frequency employed prior to the FPV. Protocol dose modification and stopping criteria are to be followed while a patient is receiving cediranib and/or olaparib. Restrictions regarding concomitant medications (Section 7.7) must be followed while the patient is receiving cediranib and/or olaparib. A change in the dose/schedule of cediranib and/or olaparib should only occur for safety reasons, based on the Investigator's judgement, and should generally follow the approach for dose reduction and discontinuation as described in this protocol. Combining cediranib and/or olaparib with other anti-cancer therapy is not allowed.

If in the opinion of the Investigator, a patient is no longer receiving clinical benefit from the IPs beyond the FPV, then the IPs will be stopped. The Investigator will inform AstraZeneca when a patient discontinues the IPs. Patients must return unused medication during routine clinic visits; drug accountability information must continue to be collected in patient source documents until the patient discontinues treatment. Patients will continue to be monitored for all SAEs and pregnancies while receiving IPs and for 30 days after the last dose of IPs.

9.4 Data management by AstraZeneca

Data management will be performed by AstraZeneca Data Management Centre staff according to the Data Management Plan.

Adverse events and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the AstraZeneca Drug Dictionary. All coding will be performed by the Medical Coding Team at the AstraZeneca Data Management Centre.

The data collected through third party sources will be obtained and reconciled against study data.

Data queries will be raised for inconsistent 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.

Serious Adverse Event (SAE) Reconciliation

SAE reconciliation reports are produced and reconciled with the Patient Safety database and/or the investigational site.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH GCP, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

10.2 Patient data protection

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.

AstraZeneca will not provide individual genotype results to patients, any insurance company, any employer, their family members, general physician or any other third party, 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)/ Institutional Review Board (IRB) should approve the final study protocol, including the final version of the Informed Consent Form 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/IRB and to the study site staff.

The opinion of the EC/IRB should be given in writing. The Investigator should submit the written approval to AstraZeneca before enrollment of any patient into the study.

The EC/IRB 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 protocol should be re-approved by the EC/IRB annually.

Before enrollment of any patient into the study, the final 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.

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide Regulatory Authorities, EC/IRB and the PI(s) at each center with safety updates/reports according to local requirements.

Each PI is responsible for providing the EC/IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the IPs. AstraZeneca will provide this information to the PI(s) so that he/she can meet these reporting requirements.

10.4 Informed consent

The PI(s) at each center 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 they are free to discontinue from the study at any time

- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided
- 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
- 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/IRB.

10.5 Changes to the 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 study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol (Revised CSP).

The amendment is to be approved by the relevant EC/IRB and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each PI(s). For distribution to EC/IRB see Section 10.3.

If a protocol amendment requires a change to a center's Informed Consent Form, AstraZeneca and the center's EC/IRB are to approve the revised Informed Consent Form before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each EC/IRB.

10.6 Audits and inspections

Authorized representatives of AstraZeneca, a regulatory authority, or an EC may perform audits or inspections at the center, 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, analyzed, and accurately reported according to the protocol, ICH GCP and any applicable regulatory requirements. The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the center.

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Appendix A Signatures

This Clinical Study Protocol has been subjected to an internal AstraZeneca peer review and is electronically signed in the AstraZeneca Document Management System by the following people:

PPD Director Clinical Development

PPD Statistical Science Director

PPD Global Clinical Leader (Physician)

PPD Project Physician

Appendix B Additional Safety Information

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

Life threatening

'Life-threatening' means that the subject 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 subject'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 subject was 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 subject 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 subject 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 and includes any toxicities considered related, probably related, or possibly related to the drug.

Appendix C 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 **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm).** For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (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 trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)**
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable

- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

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

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.

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.

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

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

DEFINITIONS

Potential Hy's Law (PHL)

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

Hy's Law (HL)

AST or ALT ≥ 3x ULN **together with** TBL ≥ 2xULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (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.

IDENTIFICATION OF POTENTIAL HY'S LAW CASES

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

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

The Investigator will remain vigilant for local laboratory reports where the identification criteria are met, where this is the case the Investigator will:

- Notify the AstraZeneca representative
- Request a repeat of the test (new blood draw)
- Complete the appropriate unscheduled laboratory CRF module(s) with the original local laboratory test result

When the identification criteria are met from the local laboratory results the Investigator will without delay:

- Determine whether the patient meets PHL criteria (see Section 0 of this Appendix for definition) by reviewing laboratory reports from all previous visits
- 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 0 of this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

FOLLOW-UP

Potential Hy's Law Criteria not met

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

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

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 0)
- Notify the AstraZeneca representative who will then inform the central Study Team

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
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which the tests available in the Hy's law lab kit should be used
- Complete the three Liver CRF Modules as information becomes available
- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

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.

No later than 3 weeks 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. The AstraZeneca Medical Science Director 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.

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

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF

- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the AZ 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:

- Report an 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 3 weeks, 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:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review

ACTIONS REQUIRED WHEN POTENTIAL HY'S LAW CRITERIA ARE MET BEFORE AND AFTER STARTING STUDY TREATMENT

This section is applicable to patients 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 is 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.

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 0?

If No: follow the process described in Section 4.2 of 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

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Appendix E Example of Performance Status (Eastern Cooperative Oncology Group [ECOG]/Karnofsky Scale)

EXAMPLE OF PERFORMANCE STATUS (ECOG/KARNOFSKY SCALE)

Table 19 ECOG/Karnofsky Scale

Description	ECOG Grade	Karnofsky Equivalent	
Fully active, able to carry on all pre-disease performance without restriction	0	100	Normal, no complaints; no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease
Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature ie, light housework, office work	1	80	Normal activity with effort; some signs or symptoms of disease
		70	Cares for self but unable to carry on normal activity or to do work.
Ambulatory and capable of self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	2	60	Requires occasional assistance but is able to care for most of personal needs.
		50	Requires considerable assistance and frequent medical care.
Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	3	40	Disabled; requires special care and assistance.
		30	Severely disabled; hospitalisation is indicated although death not imminent.
Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	4	20	Very ill; hospitalisation and active supportive care necessary.
		10	Moribund.

Appendix F Guidelines for Evaluation of Objective Tumour Response Using RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumours)

INTRODUCTION

This appendix details the implementation of Response Evaluation Criteria In Solid Tumours (RECIST) 1.1 guidelines (Eisenhauer et al 2009) for the D8488C00001 study with regards to the Investigator assessment of tumour burden including protocol-specific requirements for this study.

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 1 measurable lesion that has not been previously irradiated.

Measurable:

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

Non-measurable:

- All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 mm to <15 mm short axis at baseline[1]).
- 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.
- Lesion biopsied per the protocol prior to randomisation
- Previously irradiated lesions[2]

[1] Nodes with <10 mm short axis are considered non-pathological and should not be recorded or followed as non-target lesions (NTLs).
[2] 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 NTL at baseline and followed up as part of the NTL assessment.

- Skin lesions assessed by clinical examination
- Brain metastasis.

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 (TLs).

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 TLs at baseline.

Non-target lesions:

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline.

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 in Table 20.

Table 20 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

CT Computed tomography; FDG-PET 18-Fluoro-deoxyglucose positron emission tomography; MRI Magnetic resonance imaging.

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 D8488C00001 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 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.

Clinical examination

In the D8488C00001 study, clinical examination will not be used for assessment of TL. Clinically detected lesions can be selected as TLs 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.

Chest X-ray

In the D8488C00001 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.

Plain X-ray

In the D8488C00001 study plain X-ray may be used as a method of assessment for bone NTL and to identify the presence of new bone lesions.

Ultrasound

In the D8488C00001 study, ultrasound examination will not be used for assessment of TL and NTL as it is not a reproducible method, does not provide an accurate assessment of tumour size and it is subjective and operator dependent. Ultrasound examination can, however, be used to identify the presence of new lesions. If new clinical symptoms occur and an ultrasound is performed then new lesions should be confirmed by CT or MRI examination.

Endoscopy and laparoscopy

In the D8488C00001 study, endoscopy and laparoscopy will not be used for tumour assessments as they are not validated in the context of tumour assessment.

Tumour markers

In the D8488C00001 study tumour markers will not be used for tumour response assessments as per RECIST 1.1.

Cytology and histology

In the D8488C00001 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.

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 the baseline assessment.

In the D8488C00001 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.

FDG-PET scan

In the D8488C00001 study, 18-Fluoro-deoxyglucose positron emission tomography (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 18-Fluoro-deoxyglucose uptake[3] 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.

TUMOUR RESPONSE EVALUATION

Schedule of evaluation

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

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 within the 28 days prior to randomisation and ideally as close as possible before the start of study treatment (see the Schedule of Assessments [Table 5] in the main body of the protocol). Follow-up assessments will be performed every 8 weeks (±1 week), relative to first dose of investigational product(s) until confirmed objective disease progression as defined by RECIST 1.1 (irrespective of the reason for stopping treatment and/or subsequent therapy).

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.

Target lesions

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 millimetres. 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 >5 mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.

If a lesion has completely disappeared, the longest diameter should be recorded as 0 mm.

If a TL splits into 2 or more parts, then record the sum of the diameters of those parts.

If 2 or more TLs merge then the sum of the diameters of the combined lesion should be recorded for 1 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, during the study, the size of the TL should still be provided where possible.

Evaluation of target lesions

This section provides the definitions of the criteria used to determine objective tumour visit response for TL (see Table 21).

Table 21 Evaluation of target lesions

Complete Response (CR)	Disappearance of all TLs since baseline. Any pathological lymph nodes selected as TLs 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
Progression of disease (PD)	At least a 20% increase in the sum of diameters of TLs, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.
Not Evaluable (NE)	Only relevant if any of the TLs 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 TL response

CR Complete response; PR Partial response; PD Progression of disease; NE Not evaluable; SD Stable disease; TL Target lesion.

Non-target lesions

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 (see Table 22).

Table 22 Evaluation of non-target lesions

Complete response (CR)	Disappearance of all NTLs since baseline. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non CR/Non PD	Persistence of 1 or more NTL.
Progression of disease (PD)	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in 1 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 1 or some of the NTLs were not assessed and, in the Investigator's opinion, they are not able to provide an evaluable overall NTL assessment at this visit.

CR Complete response; PR Partial response; PD Progression of disease; NE Not evaluable; NTL Non-target lesion.

To achieve 'unequivocal progression' on the basis of NTLs, there must be an overall level of substantial worsening in non-target disease such that, even in presence of stable disease or partial response in TLs, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of 1 or more NTLs is usually not sufficient to qualify for unequivocal progression status.

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.

Symptomatic deterioration

Symptomatic deterioration is not a descriptor of an objective response: it may be 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.

Evaluation of overall visit response

The overall visit response will be derived using the algorithm shown in Table 23.

Table 23 Overall visit response

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	N/A	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, N/A not applicable (only if relevant if there were no NTL at baseline)

CONFIRMATION OF PROGRESSION

While disease progression may require confirmation, it is not mandated in this study. Confirmation will be subject to the investigator's discretion (eg. if investigator is not sure of progression at initial assessment). The confirmatory scan should occur preferably at the next scheduled visit and no earlier than 4 weeks after the initial assessment of progression of disease (PD) in the absence of clinical deterioration.

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.

CONFIRMATION OF RESPONSE

In Study D8488C00001, imaging for confirmation of response (CR or PR) should be performed at the next scheduled RECIST assessment, 8 weeks (certainly no less than 4 weeks) following the date the criteria for response were first met.

CENTRAL REVIEW

The Contract Research Organisation appointed by AstraZeneca to perform the independent central review for the primary analysis of this study will provide specification for radiological imaging protocols in standard acquisition guidelines documentation.

REFERENCES

Eisenhauer et al 2009
Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-47.

Appendix G Hypertension Medication

The following anti-hypertensive medications have been provided as a guide and those used in this study will depend upon local practice.

Note: Agents in bold characters are suggested as optimal choices to avoid or minimize potential drug-interactions with cediranib through cytochrome P450 (CYP450)

Table 24 Dihydropyridine calcium-channel blockers

Agent	Initial dose	Intermediate dose	Maximum dose	Hepatic metabolism?
Nifedipine XL	30 mg po qd	60 mg po qd	90 mg po qd	CYP 3A4 substrate
Amlodipine	2.5 mg po qd	5 mg po qd	10 mg po qd	CYP 3A4 substrate
Felodipine	2.5 mg po qd		10 mg po qd	CYP 3A4 substrate + inhibitor

Abbreviations: po oral; qd once daily

Table 25 Selective beta-blockers

Agent	Initial dose	Intermediate dose	Maximum dose	Hepatic metabolism?
Metoprolol	25 mg po bd	50 mg po bd	100 mg po bd	CYP2D6 substrate
Atenolol	25 mg po qd	50 mg po qd	100 mg po qd	No
Acebutolol	100 mg po bd	200-300 mg po bd	400 mg po bid	Yes (CYP450 questionable)
Bisoprolol	2.5 mg po qd	5-10 mg po bd	20 mg po qd	Yes (CYP450 questionable)

Abbreviations: bd twice daily; po oral; qd once daily

Table 26 Angiotensin Converting Enzyme Inhibitors (ACEIs)

Agent	Initial dose	Intermediate dose	Maximum dose	Hepatic metabolism?
Captopril	12.5 po tid	25 mg po tid	50 mg po tid	CYP 2D6 substrate
Enalapril	5 mg po qd	10-20 mg po qd	40 mg po qd	CYP 3A4 substrate
Ramipril	2.5 mg po qd	5 mg po qd	10 mg po qd	Yes (CYP450 questionable)
Lisinopril	5 mg po qd	10-20 mg po qd	40 mg po qd	No
Fosinopril Rarely used:	10 mg po qd	20 mg po qd	40 mg po qd	Yes (CYP450 questionable)
Perindopril	4 mg po qd	none	8 mg po qd	Yes but not per CYP450
Quinapril	10 mg po qd	20 mg po qd	40 mg po qd	No

Abbreviations: po oral; tid three times daily; qd once daily

Table 27 Angiotensin II Receptors Blockers (ARBs)

Agent	Initial dose	Intermediate dose	Maximum dose	Hepatic metabolism?
Losartan	25 mg po qd	50 mg po qd	100 mg po qd	CYP3A4 substrate
Candesartan	4 mg po qd	8-16 mg po qd	32 mg po qd	CYP2C9 substrate
Irbesartan	75 mg po qd	150 mg po qd	300 mg po qd	CYP2C9 substrate
Telmisartan	40 mg po qd	none	80 mg po qd	Yes but not per CYP450
Valsartan	80 mg po qd	none	160 mg po qd	Yes but not per CYP450

Abbreviations: po oral; qd once daily

Table 28 Alpha and beta-blocker

Agent	Initial dose	Intermediate dose	Maximum dose	Hepatic metabolism?
Labetolol	100 mg po bid	200 mg po bd	400 mg po bd	CYP 2D6 substrate and inhibitor

Abbreviations: bd twice daily; po oral


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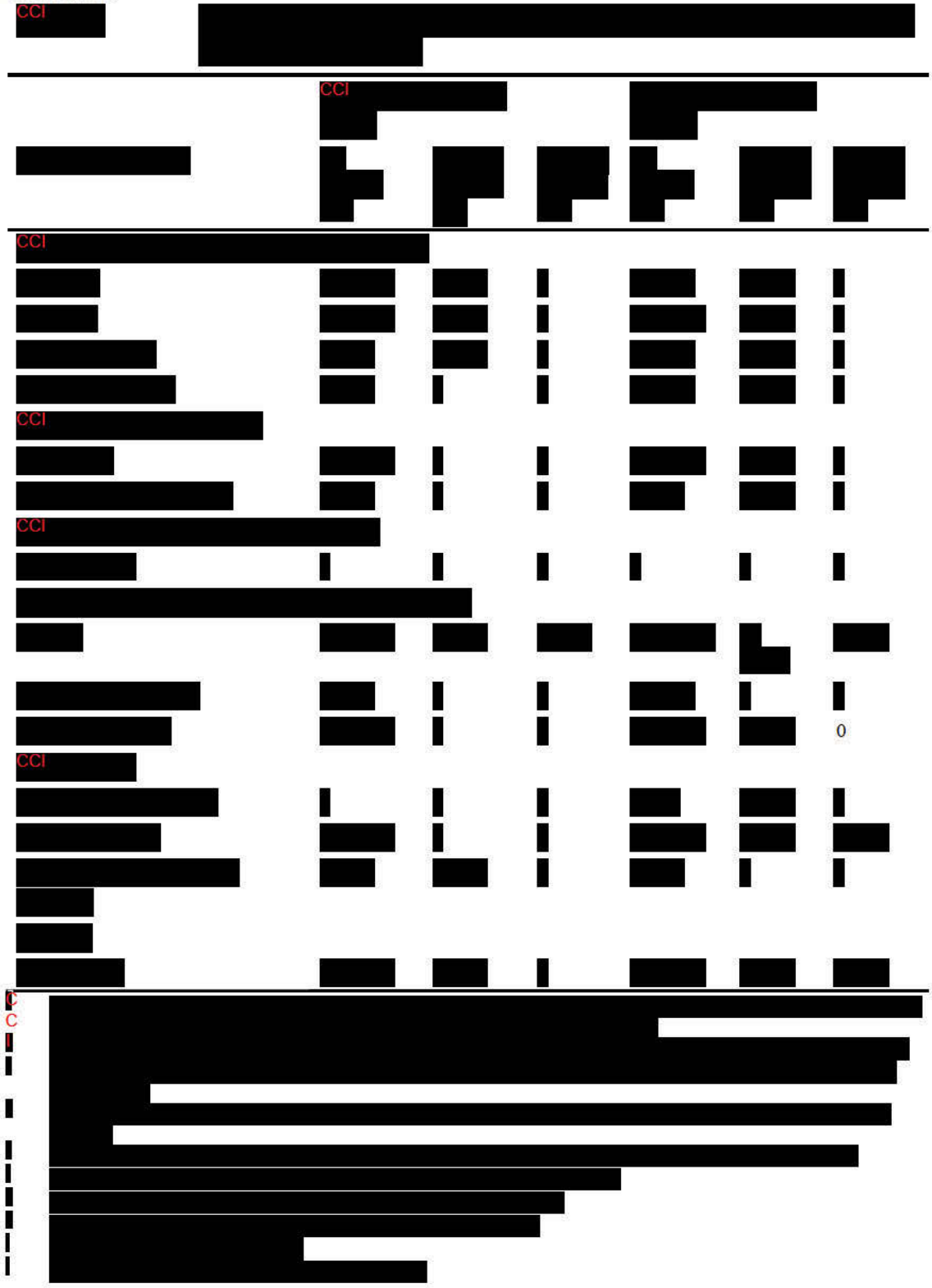
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Appendix I List of CYP3A4 inhibitors and inducers

GUIDANCE REGARDING POTENTIAL INTERACTIONS WITH CONCOMITANT MEDICATIONS

Note. While this is not an exhaustive list, it covers the known potent inhibitors and inducers, which have most often previously been reported to be associated with clinically significant drug interactions. Please contact the Medical Monitor or AstraZeneca physician if further clarification is required. For a more detailed list of CYP3A4 inhibitors/inducers, please visit FDA website:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#4

INTERACTIONS WITH P450:

Olaparib is substrate of CYP3A4. Therefore, CYP3A4 inhibitors and inducers will affect olaparib's exposure. Cediranib is not substrate of CYP3A4, but it is substrate of UGT and PgP. Some CYP3A4 inhibitors and inducers also inhibit or induce UGT/Pgp.

POTENT INHIBITORS OF CYP3A4:

The following inhibitors of CYP3A4 must not be used during this study:

Table 30 Potent inhibitors of CYP3A4

Drug	Minimum washout period prior to starting IP
Ketoconazole; Itraconazole; Indinavir; Saquinavir; Telithromycin; Nelfinavir; Clarithromycin; Ritonavir; Cobicistat; Indinavir; Saquinavir; Nelfinavir; Boceprevir; Telaprevir and Clarithromycin	2 Weeks

Moderate CYP3A inhibitors (eg. ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil) should be avoided with at least 1 week washout period.

INDUCERS OF CYP3A4:

In addition, to avoid potential reductions in exposure due to drug interactions, the following CYP3A4 inducers should be avoided:

Table 31 Potent inducers of CYP3A/4

Drug	Minimum washout period prior to starting IP
Carbamazepine; Modafinil; Nevirapine; Phenytoin; Rifabutin; Rifampicin; Rifapentin; St John's Wort (Hypericum perforatum); Bosentan; Efavirenz; Modafinil.	4 Weeks
Phenobarbitone; Enzalutamide	5 Weeks

After recruitment, if the use of any potent inducers or inhibitors of CYP3A4 are considered necessary for the patient's safety and welfare, the investigator must contact the AstraZeneca Study Physician. A decision to allow the patient to continue in the study will be made on a case-by-case basis.

NATURAL / HERBAL PRODUCTS:

The use of any natural/herbal products or other "folk 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 appropriate eCRF.

Appendix J Acceptable Birth Control Methods

OLAPARIB AND CEDIRANIB ARE REGARDED AS COMPOUNDS WITH 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], throughout the period of taking study treatment and for at least 6 weeks after last dose of study drug(s), or they must totally/truly abstain from any form of sexual intercourse (see below).

ACCEPTABLE NON-HORMONAL BIRTH CONTROL METHODS INCLUDE:

- Total sexual abstinence. Abstinence must continue for the total duration of study treatment and for at least 1 month after the last dose. Periodic abstinence (eg, calendar ovulation, symptothermal post ovulation methods) 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
- IUD 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 / EE transdermal system PLUS male condom
- Intrauterine system [IUS] device (eg, levonorgestrel releasing IUS -Mirena®) PLUS male condom
- Intravaginal device (eg, EE and etonogestrel) PLUS male condom.

Appendix K PRO questionnaires (EORTC QLQ-C30, QLQ OV28, and PRO-CTCAE)

EORTC QLQ-C30

(version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year):

		Not at All	A Little	Very a Bit	Quite Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

		Not at All	A Little	Very a Bit	Quite Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4

10.	Did you need to rest?	1	2	3 4
11.	Have you had trouble sleeping?	1	2	3 4
12.	Have you felt weak?	1	2	3 4
13.	Have you lacked appetite?	1	2	3 4
14.	Have you felt nauseated?	1	2	3 4
15.	Have you vomited?	1	2	3 4
16.	Have you been constipated?	1	2	3 4

Please go on to the
next page

During the past week:	Not at All	Very Little	A a Bit	Quite Much
17. Have you had diarrhea?		1 4	2	3
18. Were you tired?		1 4	2	3
19. Did pain interfere with your daily activities?		1 4	2	3
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?		1 4	2	3
21. Did you feel tense?		1 4	2	3
22. Did you worry?		1 4	2	3
23. Did you feel irritable?		1 4	2	3
24. Did you feel depressed?		1 4	2	3
25. Have you had difficulty remembering things?		1 4	2	3
26. Has your physical condition or medical treatment interfered with your family life?		1 4	2	3
27. Has your physical condition or medical treatment interfered with your social activities?		1 4	2	3
28. Has your physical condition or medical treatment caused you financial difficulties?		1 4	2	3

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

EORTC QLQ - OV28

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Did you have abdominal pain?	1	2	3	4
32. Did you have a bloated feeling in your abdomen / stomach?	1	2	3	4
33. Did you have problems with your clothes feeling too tight?	1	2	3	4
34. Did you experience any change in bowel habit as a result of your disease or treatment?	1	2	3	4
35. Were you troubled by passing wind / gas / flatulence?	1	2	3	4
36. Have you felt full too quickly after beginning to eat?	1	2	3	4
37. Have you had indigestion or heartburn?	1	2	3	4
38. Have you lost any hair?	1	2	3	4

39. Answer this question only if you had any hair loss:

	Were you upset by the loss of your hair?	1	2	3	4
40.	Did food and drink taste different from usual?	1	2	3	4
41.	Have you had tingling hands or feet?	1	2	3	4
42.	Have you had numbness in your fingers or toes?	1	2	3	4
43.	Have you felt weak in your arms or legs?	1	2	3	4
44.	Did you have aches or pains in your muscles or joints?	1	2	3	4
45.	Did you have problems with hearing?	1	2	3	4
46.	Did you urinate frequently?	1	2	3	4
47.	Have you had skin problems (e.g. itchy, dry)?	1	2	3	4
48.	Did you have hot flushes?	1	2	3	4
49.	Did you have night sweats?	1	2	3	4

Please go on to next page

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
50. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
51. Have you been dissatisfied with your body?	1	2	3	4
52. How much has your disease been a burden to you?	1	2	3	4
53. How much has your treatment been a burden to you?	1	2	3	4
54. Were you worried about your future health?	1	2	3	4

During the past 4 weeks:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
55. To what extent were you interested in sex?	1	2	3	4
56. To what extent were you sexually active?	1	2	3	4
Answer the following two questions only if you were sexually active:				
57. To what extent was sex enjoyable for you?	1	2	3	4
58. Did you have a dry vagina during sexual activity?	1	2	3	4

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0

As individuals go through treatment for their cancer, they sometimes experience different symptoms and side effects. For each question, please check or mark an ☒ in the one box, that best describes your experiences over the past 7 days…

1.	In the last 7 days, what was the SEVERITY of your DECREASED APPETITE at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did DECREASED APPETITE INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

2.	In the last 7 days, how OFTEN did you have NAUSEA?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

3.	In the last 7 days, how OFTEN did you have VOMITING?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your VOMITING at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

4.	In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA)?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly

5.	In the last 7 days, what was the SEVERITY of your DIZZINESS at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did DIZZINESS INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

PRO-CTCAE ADDITIONAL QUESTION

	In the last 7 days, how MUCH did LOOSE OR WATERY STOOLS (DIARRHEA) INTERFERE with your usual or daily activities?"				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly

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