AstraZeneca

Clinical Study Protocol

Drug Substance	Olaparib
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Version	3.0
Date	10 October 2017

Non-Randomized, Open-Label Phase II Study to Assess Olaparib Tablets as a Treatment for Subjects with Different HRD Tumor Status and with Platinum-Sensitive, Relapsed, High-Grade Serous or High-Grade Endometrioid Ovarian, Fallopian Tube, or Primary Peritoneal Cancer That Have Received at Least 1 Prior Line of Chemotherapy

Sponsor: AstraZeneca Pharmaceuticals LP, 1800 Concord Pike, Wilmington, DE 19809

VERSION HISTORY

Version 1.0, 01 September 2016
Initial creation.
Version 2.0, 01 March 2017 Changes to the protocol are summarized below:
Synopsis: The number of sites was increased from approximately 25 sites to approximately 40 sites and Canada was added as a site location. Synopsis, Section 1.4: The number of potential subjects enrolled was changed from 120 to up to approximately 300 subjects. Approximately 450 subjects will be screened to identify up to approximately 300 subjects to be enrolled in the 4 cohorts which will include at least 30 subjects each. Cohorts may continue enrollment up to 90 subjects each (unless early stopping criteria are met) at which point that cohort will be closed to further enrollment. Once all 4 cohorts have at least 30 subjects (unless early stopping criteria are met), the study will be closed to further enrollment. Synopsis, Section 2.2, Section 8.4.3.1, and Section 8.4.3.3: The text was modified to clarify that for those subjects with a confirmed response of complete response (CR) or partial response (PR), response duration will be measured from the date of the measurement criteria for CR or PR are first met until the date of documented objective progression or death in the absence of disease progression. Additionally, text was modified to clarify that disease control rate is defined as the percentage of subjects with a best overall response of confirmed CR or PR (at any time up to and including the defined analysis cut off point) or who have demonstrated stable disease for at least 8 weeks from first dose, divided by the number of subjects in the efficacy analysis set. CCI [redacted]. Synopsis, Section 3.5, and Section 4: Cohort enrollment stopping rules were added. The enrollment stopping rules state that objective response will be monitored on an ongoing basis for subjects in each cohort. If no responses (complete response or partial response) are observed in the first 15 subjects in a cohort, in consultation with the Steering Committee, this cohort will be closed to further enrollment. However, if there is at least 1 confirmed objective response in the first 15 subjects, that would justify continuing enrollment up to a maximum of 90 subjects. This stopping rule applies to all cohorts. Enrollment in each cohort will continue while objective response is being assessed for the futility assessment. The objective response will be assessed as per protocol, i.e., allowing 6 months of follow up. The Myriad testing may be submitted in advance of the 28-day screening window if the subject consents to the appropriate pre-screening informed consent form. Synopsis, Section 3.9.1, Section 4: The text was modified to clarify that at the end of the additional 12 months of survival follow-up, updated overall survival and safety analyses will be conducted and the study will be closed.

Synopsis and Section 8.2: The sample size text was modified to reflect the changes in cohort enrollment (minimum of 30 subjects, maximum of 90 subjects per cohort).

Synopsis and Section 9.3: The anticipated enrollment duration was reduced from 30 months to approximately 20 months.

Section 3.5, Section 4.1, and Section 5.6.1: The protocol was revised to state that prior to any cohorts being closed to enrollment, subjects may enroll in the study and initiate treatment prior to the Myriad BRACAnalysis CDx® and myChoice® homologous recombination deficiency (HRD) tests being reported; however, subjects will not be allocated into a cohort until the results are received by the Investigator. Once the test results are received by the Investigator, the subject will be allocated into the appropriate cohort. Once a cohort reaches 90 subjects, the cohort will be closed, and subjects may not initiate treatment until their Myriad BRACAnalysis CDx® and myChoice® HRD tests are completed, the results are received by the Investigator, and it is confirmed an open-cohort is available for which the subject is eligible.

Section 4, Table 4, Section 4.1, Section 5.6.1: A pre-screening option was added. The Myriad testing may be submitted in advance of the 28-day screening window if the subject consents to the appropriate pre-screening informed consent form.

Table 4, Section 4.2.1, Section 4.2.5, Section 5.6.1, Section 5.6.5, Table 6, and Section 8.4.6: Collection of mandatory blood samples for circulating tumor deoxyribonucleic acid analysis was added at baseline and disease progression.

Section 3.9, Section 4, Section 4.2.5, and previous Section 4.3.1: The text was revised and deleted as necessary to clarify that subjects must be discontinued from the active study treatment phase if they have objective radiological disease progression according to Response Evaluation Criteria in Solid Tumors v1.1.

Section 4.3.2: Text was modified to clary that follow-up after the final data cut-off refers to the final data cut-off for the primary endpoint analysis.

Section 1.4 and Section 5.6.1: It was clarified that additional tumor samples (10 to 20 slides) will also be collected for a mandatory tumor biopsy at screening and at objective radiological disease progression, if there is a tumor that can be biopsied and it is not clinically contraindicated.

Section 8.5.4, An informal interim analysis was added. The informal interim analysis in each cohort will take place after 15 subjects have had at least 1 radiologic tumor response assessment in the first 6 months of the study. If no responses (CR or PR) are observed in the first 15 subjects in a cohort, in consultation with the Steering Committee, the cohort will be closed to further enrollment. However, if there is at least 1 confirmed objective response in the first 15 subjects, that would justify continuing enrollment up to a maximum of 90 subjects. Enrollment will continue until these interim analyses have been completed and a decision is made by the Study Steering Committee. Additionally annual updates of relevant study data may be generated for the purpose of reporting at appropriate oncology conferences, as specified in the statistical analysis plan.

The stopping boundary for the interim futility analysis was determined from the binomial probabilities. With a true objective response rate (ORR) of 5%, a cohort would terminate early for futility (no responders observed in the first 15 subjects) with a probability of 0.463, while with true ORRs of 10%, 20%, 40%, and 50%, a cohort would terminate early for futility with probabilities of 0.206, 0.0352, 0.0005, and < 0.0001, respectively. Section 3.8.2: Language was added to the contraception text to include the partners of women of childbearing potential to be consistent with updates to the Investigator's brochure. Section 7.3: Minor changes were made to the standard labeling text. The Study Plan (Table 4) was revised to be consistent with the changes in this amendment. Minor edits were made throughout the document to correct grammatical errors and inconsistencies.
Version 3.0, 10 October 2017
The protocol was amended to reflect the use of PARP inhibitors as an effective treatment option for women with ovarian cancer being utilized for patients with fewer previous lines of therapy. Studies have shown PARP inhibitors in second-line therapy for recurrent ovarian cancer thereby have objective response rates similar to standard chemotherapy. Title, Synopsis, Section 3.1 and 4: Inclusion criterion #3 was revised to include high-grade endometrioid cancer. Title, Synopsis, Sections 1.3.1, 1.4, 3.1, and 4: Inclusion criterion #5 was revised to enroll subjects who have received at least 1 prior platinum-based line of chemotherapy for ovarian cancer, rather than the previous 2 prior platinum-based lines of chemotherapy. Section 3.1: Inclusion criterion #7 was revised in Section 3.1 to "Subjects must have serum creatinine ≤ 1.5 × ULN, OR creatinine clearance estimated using the Cockcroft-Gault equation of ≥ 51 mL/min. Subjects with severe renal impairment (CrCl ≤ 30 mL/min) are excluded, regardless of measured serum creatinine." from "Subjects must have creatinine clearance estimated using the Cockcroft-Gault equation of ≥ 51 mL/min." Section 6.7.2.3: For consistency with the revised Inclusion criterion #7, the language was revised to clarify that "If subsequent to study entry and while still on study therapy, a subject's estimated creatinine clearance (CrCl) decreases to become < 51 mL/min, retesting should be performed promptly. A dose reduction is recommended for subjects who meet the following criteria during the course of the study: Baseline CrCl ≥ 51 mL/min who have on study a CrCl < 51 mL/min, or Baseline CrCl < 51 mL/min but had serum creatinine ≤ 1.5 × ULN, and then on study had a clinically meaningful lower CrCl value. The dose of olaparib should be reduced to 200 mg bid. Olaparib has not been studied in subjects with

severe renal impairment (CrCl ≤ 30 mL/min) or end-stage renal disease; if subjects develop severe impairment or end-stage renal disease olaparib must be discontinued."

Sections 1.1, 1.2, 1.2.1, 1.3.2, and 1.3.2.1: Text was updated to reflect the approval of the olaparib tablet formulation, as well as results from Study 19 and SOLO-2, as appropriate.

Section 3.8.2 and Appendix E: The duration of contraception requirements was clarified and language was modified to clarify the contraception requirements should be started from the signing of informed consent.

Section 4.2.5 and Table 6 (Study Plan): The visit window for the study discontinuation visit was corrected from ± 7 days to + 7 days.

Appendix E: Acceptable non-hormonal birth control methods were clarified. The definition of abstinence was modified to "Acceptable non-hormonal birth control methods include: Total/True abstinence: When the subject refrains from any form of sexual intercourse and this is in line with their usual and/or preferred lifestyle; this must continue for the total duration of the trial and for at least 1 month after the last dose of study drug. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods, or declaration of abstinence solely for the duration of a trial) and withdrawal are not acceptable methods of contraception;" from "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 for female subjects. Periodic abstinence (e.g., calendar ovulation, symptothermal post-ovulation methods) and withdrawal are not acceptable methods of contraception."

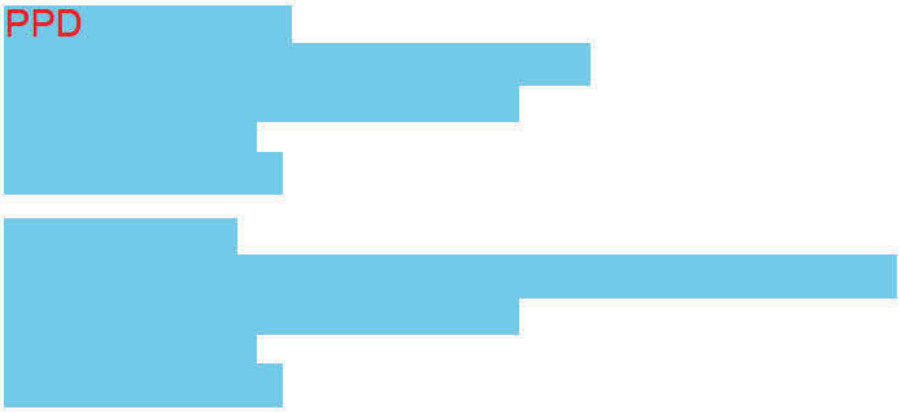
Table 6 (Study Plan) and Section 5.2.5.1: The pregnancy testing requirements were modified to add testing at Day 29 and at regular intervals (monthly).

Minor edits were made throughout the document to correct grammatical errors and inconsistencies.

PROTOCOL SYNOPSIS

Non-Randomized, Open-Label Phase II Study to Assess Olaparib Tablets as a Treatment for Subjects with Different HRD Tumor Status and with Platinum-Sensitive, Relapsed, High-Grade Serous or High-Grade Endometrioid Ovarian, Fallopian Tube, or Primary Peritoneal Cancer That Have Received at Least 1 Prior Line of Chemotherapy

National Coordinating Investigators



Study sites and number of subjects planned

This will be a multi-center study at approximately 40 sites, with more sites to be added as required to complete enrollment, in the United States (US) and Canada.

Approximately 450 subjects will be screened to identify up to approximately 300 subjects to be enrolled in 4 cohorts which will include at least 30 subjects in each. An individual cohort may continue enrollment up to 90 subjects (unless early stopping criteria are met) at which point the cohort will be closed to further enrollment. Once all 4 cohorts have at least 30 subjects, the study will be closed to further enrollment.

Study period		Phase of development
Estimated date of first subject enrolled	Q4 2016	II
Estimated date of last subject completed	Q1 2020	II

The anticipated enrollment period is approximately 20 months. A data cut-off for analysis of all primary and secondary endpoints will occur approximately 6 months after the last subject enrolled has commenced study treatment (received at least 1 dose of olaparib). The study will remain open for an additional 12 months after this data cut-off for survival follow-up for

applicable subjects. At the end of this additional 12 months of survival follow-up, updated overall survival (OS) and safety analyses will be conducted and the study will be closed.

Study design

This is a Phase II, open-label, non-randomized, multi-center study assessing the efficacy and safety of olaparib tablets 300 mg CCI in subjects with platinum-sensitive or partially platinum-sensitive, relapsed, high-grade serous or high-grade endometrioid ovarian, fallopian tube, or primary peritoneal cancer, who have received at least 1 prior line of platinum-based chemotherapy.

The study will assess the effectiveness of olaparib tablets as measured by the objective response rate (ORR) as determined by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, in subjects with germline BRCA mutations (gBRCAm), somatic BRCA mutations (sBRCAm), or potential aberrations in homologous recombination deficiency (HRD) as determined by myChoice® HRD, as well as in subjects without identifiable HRD. This study will utilize Myriad BRACAnalysis CDx® for germline BRCA analysis and a tumor test (myChoice® HRD) for tumor BRCA analysis and HRD status. Note: The Myriad testing may be submitted in advance of the 28-day screening window if the subject consents to the appropriate pre-screening informed consent form.

Four cohorts will be identified based upon the genetic testing described above:

- Cohort 1: gBRCAm,
- Cohort 2: sBRCAm and germline BRCA wild type,
- Cohort 3: myChoice® HRD positive (genomic instability positive) and BRCA wild type (BRCAwt) (no BRCA mutation),
- Cohort 4: myChoice® HRD negative (genomic instability negative) and BRCAwt (no BRCA mutation).

Cohort enrollment rules:

The objective response will be monitored on an ongoing basis for subjects in each cohort. If no responses (complete response [CR] or partial response [PR]) are observed in the first 15 subjects in a cohort, in consultation with the Steering Committee, this cohort will be closed to further enrollment. However, if there is at least 1 confirmed objective response in the first 15 subjects, that would justify continuing enrollment up to a maximum of 90 subjects. This stopping rule applies to all cohorts. Enrollment in each cohort will continue while objective response is being assessed for the futility assessment. The objective response will be assessed as per protocol, i.e., allowing 6 months of follow up.

Up to approximately 300 subjects are to be treated with olaparib, unless early stopping criteria are met.

A data cut-off for analysis of all primary and secondary endpoints will occur approximately 6 months after the last subject enrolled has commenced study treatment (received at least 1 dose of olaparib). The study will remain open for an additional 12 months after this data cut-off for survival follow-up for applicable subjects. At the end of this additional 12 months of survival follow-up, updated OS and safety analyses will be conducted and the study will be closed. Subjects are, however, permitted to continue to receive olaparib beyond the closure of the database if, in the opinion of the Investigator, they are continuing to receive benefit from treatment with olaparib. During this time, adverse events of special interest and serious adverse events (SAEs) must still be collected and reported until 30 days after the subject finally stops taking olaparib.

All subjects who enrolled and received at least 1 dose of olaparib will be followed for survival. Subjects will be contacted to assess survival every 12 weeks following disease progression until death, withdrawal of consent, or study closure.

A Study Steering Committee composed of representatives from AstraZeneca and key Investigators/scientific advisors will be responsible for providing recommendations to US Medical Affairs leadership at AstraZeneca based on Investigator input, review, and oversight of study execution, scientific conduct, and analysis of study data. The accountabilities and requirements of the Steering Committee members will be outlined in the Steering Committee Charter.

Objectives

Primary Objective:	**Outcome Measure:**
To determine the clinical effectiveness of olaparib treatment in each of 4 cohorts assessed using ORR according to RECIST v1.1 criteria (Investigator determined).	• ORR, defined as the percentage of subjects with a best overall response of confirmed CR or PR (at any time up to and including the defined analysis cut-off point) divided by the number of subjects in the efficacy analysis set.

Secondary Objectives:	**Outcome Measures:**
To determine the clinical effectiveness of olaparib treatment in each of 4 cohorts assessed using: • Duration of response (DoR), • Cancer antigen (CA)-125 response rate, • Disease control rate (DCR), • Progression-free survival (PFS), • Time to any progression (TTAP), • OS, and • Homologous recombination repair mutation (HRRm) gene panel status related to clinical outcome.	• DoR, for those subjects with a confirmed response of CR or PR, response duration will be measured from the date of the measurement criteria for CR or PR are first met until the date of documented objective progression or death in the absence of disease progression. • CA-125 response rate, defined as the percentage of subjects with a CA-125 response according to Gynecological Cancer Intergroup criteria (GCIG) divided by the number of subjects evaluable for CA-125 response. • DCR, defined as the percentage of subjects with a best overall response of confirmed CR or PR (at any time up to and including the defined analysis cut-off point) or who have demonstrated stable disease for at least 8 weeks from first dose, divided by the number of subjects in the efficacy analysis set. • PFS, defined as the time from the date of the first dose of olaparib to the earlier date of assessment of objective progression (per RECIST v1.1 criteria) or death by any cause in the absence of progression. • TTAP, defined as the time from the date of the first dose of olaparib to the earlier date of CA-125 progression (GCIG criteria) or RECIST v1.1 progression, or death by any cause in the absence of progression. • OS, defined as the time from the date of the first dose of olaparib to the date of death from any cause. • HRD status as per HRRm gene panel assessment (positive or negative) will be correlated with clinical outcome (ORR, defined above) for subjects enrolled in the 2 cohorts with BRCAwt (cohorts 3 and 4).

Safety Objective:	Outcome Measures:
To assess the safety and tolerability of single agent olaparib in each of 4 cohorts.	• Any adverse events, including SAEs; physical examination; vital signs including blood pressure, pulse, and electrocardiogram; and collection of clinical chemistry/hematology parameters.

Target subject population

Eligible subjects are subjects with documented high-grade serous or high-grade endometrioid ovarian, fallopian tube, or primary peritoneal cancer, 18 years of age or older, with platinum-sensitive (defined as progression > 12 months after the end of the last platinum-based chemotherapy) or partially platinum-sensitive (defined as progression 6 to 12 months after the end of the last platinum-based chemotherapy), who have had at least 1 or more lines of platinum-based treatment with chemotherapy and have measurable disease.

Measurable disease includes at least 1 lesion that can be accurately assessed at baseline by computed tomography/magnetic resonance imaging and is suitable for repeated assessment.

Approximately 450 subjects will be screened to identify up to approximately 300 subjects to be enrolled in 4 cohorts which will include at least 30 subjects in each. An individual cohort may continue enrollment up to 90 subjects (unless early stopping criteria are met) at which point the cohort will be closed to further enrollment. Once all 4 cohorts have at least

30 subjects (unless early stopping criteria are met), the study will be closed to further enrollment. All subjects enrolled in a cohort will receive olaparib tablets 300 mg CCI [redacted] CCI [redacted] continuously.

Duration of treatment

Subjects will continue treatment with olaparib tablets 300 mg CCI [redacted], from enrollment (Visit 2) until objective radiological disease progression as per RECIST v1.1 as assessed by the Investigator, or when they meet any discontinuation criteria (see Section 3.9).

All subjects who enrolled and received at least 1 dose of olaparib will be followed for survival. Subjects will be contacted to assess survival every 12 weeks following disease progression until death, withdrawal of consent, or study closure.

Investigational product, dosage, and mode of administration

Subjects will be administered olaparib orally at 300 mg CCI [redacted] Olaparib tablets should be taken at the same time each day, approximately 12 hours apart, with 1 glass of water. The tablets should be swallowed whole and not chewed, crushed, dissolved, or divided. Olaparib can be taken with or without food.

See Section 6.7 and Table 9 for details on olaparib-related toxicities and dose reduction.

Statistical methods

Sample size

This is a non-comparative Phase II study and each of the 4 cohorts will be analyzed separately; no statistical comparison will be made between the cohorts. Based upon the precision estimates, it was determined that a target sample size of at least 30 subjects per cohort will provide an adequate level of confidence in the estimated ORR for the purpose of the current study. However, given the estimated frequency of subjects expected to be identified in each genetic cohort it is feasible that up to 90 subjects may be enrolled in each of cohorts 1, 3, and 4 by the time enrollment to cohort 2 (sBRCAm and gBRCAwt) has reached 30 subjects. CCI [redacted] Therefore, a total of up to approximately 300 subjects may be enrolled in the study.

Efficacy analysis set: The efficacy analysis set comprises all subjects who received at least 1 dose of olaparib and had a baseline tumor assessment.

Safety analysis set: The safety analysis set comprises all subjects who received at least 1 dose of olaparib.

Continuous data will be summarized using descriptive statistics (number of observations, mean, standard deviation, median, minimum, and maximum). Frequencies and percentages

will be used for summarizing categorical (discrete) data. Confidence intervals (CIs), when presented, will generally be constructed at the 95% level.

The ORR, DCR, and CA-125 response rate will be presented together with the exact 95% CI calculated using the Clopper-Pearson method. Time-to-event outcomes (DoR, PFS, TTAP, and OS) will be analyzed using the Kaplan-Meier method and will be presented as the median and 95% CI together with event rates at clinically relevant time points. Kaplan-Meier curves will also be generated.

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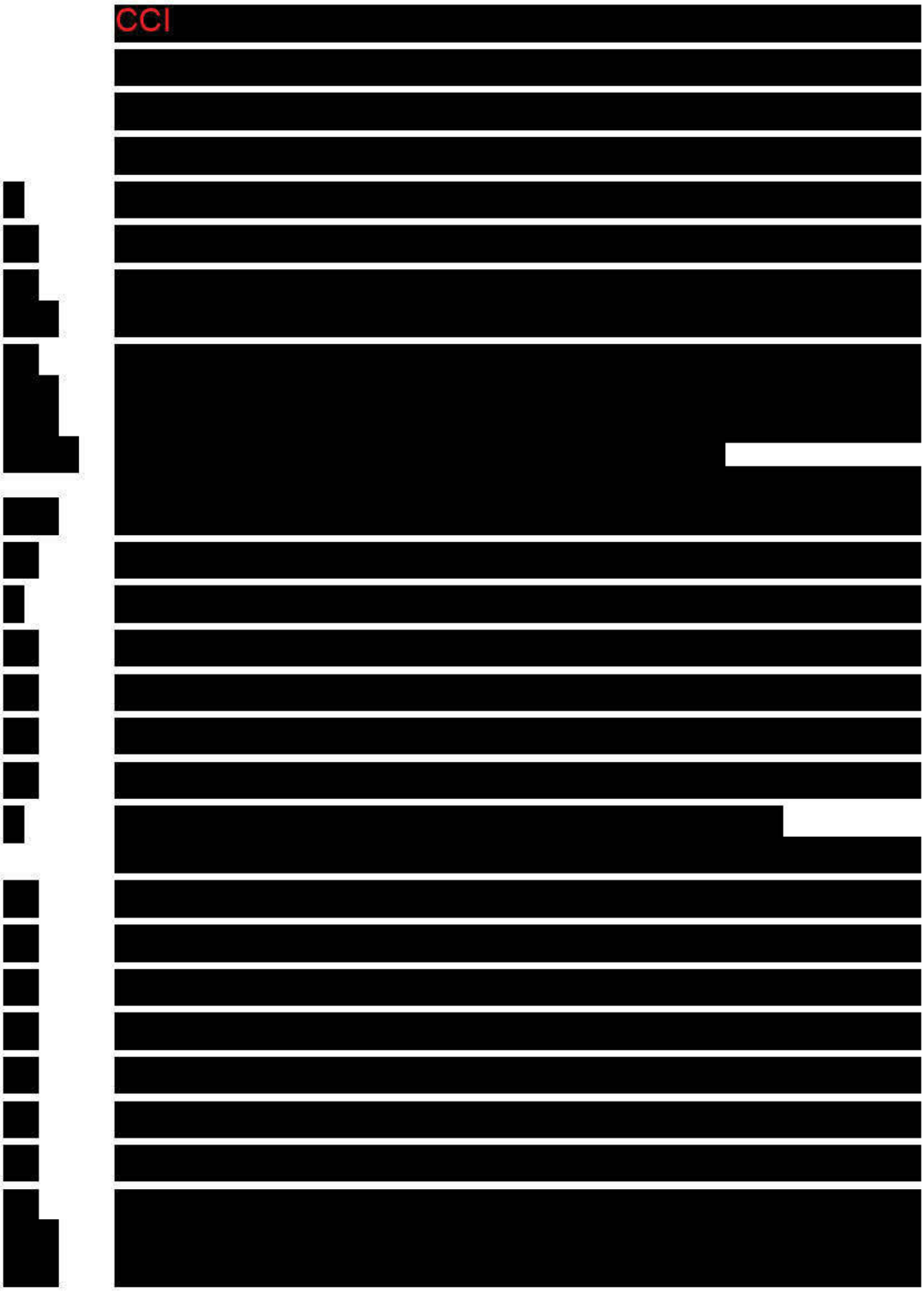

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
bid	Twice daily
BRCAm	BRCA mutation
BRCAwt	BRCA wild type
CA	Cancer antigen
CI	Confidence interval
C_{max}	Maximum concentration
C_{min}	Minimum concentration
CR	Complete response
CrCl	Creatinine clearance
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
CYP	Cytochrome P-450
DCR	Disease control rate
DNA	Deoxyribonucleic acid
DoR	Duration of response
DSB	Double-stranded break
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group: a performance status using scales and criteria to assess how a subject's disease is progressing
eCRF	Electronic case report form
EDC	Electronic data capture
FDA	Food and Drug Administration

Abbreviation or special term	Explanation
gBRCA	Germline BRCA
gBRCAm	Germline BRCA mutation
gBRCAwt	Germline BRCA wild type
GCIG	Gynecological Cancer Intergroup
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GMP	Good Manufacturing Practice
HR	Hazard ratio
HRD	Homologous recombination deficiency
HRR	Homologous recombination repair
HRRm	Homologous recombination repair mutation
IB	Investigator Brochure
ICH	International Conference on Harmonisation
INR	International normalized ratio
IP	Investigational product
IRB	Institutional review board
LIMS	Laboratory Information Management System
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NE	Not evaluable
ORR	Objective response rate
OS	Overall survival
PARP	Polyadenosine 5’diphosphoribose (poly [ADP ribose]) polymerase
PD	Progressive disease
PFS	Progression-free survival
PGx	Pharmacogenetic
PK	Pharmacokinetic
PLD	PEGylated liposomal doxorubicin
PR	Partial response
RECIST	Response Evaluation Criteria in Solid Tumors

Abbreviation or special term	Explanation
SAE	Serious adverse event
SAP	Statistical Analysis Plan
sBRCAm	Somatic BRCA mutation
SD	Stable disease
SSB	Single-stranded break
$t_{½}$	Terminal half-life
TBL	Total bilirubin
TL	Target lesion
TTAP	Time to any progression
Tumor BRCAm	Tumor BRCA mutation (composed of gBRCA or somatic BRCA mutations)
ULN	Upper limit of normal
US	United States

1. INTRODUCTION

1.1 Background and rationale for conducting this study

In 2016 in the United States (US), it is estimated that 22,290 new cases of ovarian cancer will be diagnosed and will cause 14,240 deaths (American Cancer Society, Cancer Facts and Figures 2016). Ovarian cancer is the fifth most common cause of death from cancer in women (Colombo et al 2010, NCCN Clinical Practice Guidelines in Oncology). Ovarian cancer is diagnosed predominantly in postmenopausal women with the majority of cases being diagnosed in women over 50 years of age. More than 70% of the subjects are diagnosed with advanced disease, and less than 40% of women with ovarian cancer are cured (Fleming et al 2009, Jemal et al 2010).

The standard therapy for advanced ovarian cancer consists of radical debulking surgery followed by post-operative, platinum-based, first-line chemotherapy. Although 70% to 80% of subjects respond to such initial treatment, the majority subsequently relapse; circa 75% of subjects with advanced ovarian cancer develop recurrent or progressive disease (PD) with a time lapse of circa 18 months median between first line therapy and treatment at recurrence (Ledermann and Kristleit 2010). Once relapsed, the disease is no longer considered curable. The progression free interval after the last most recent platinum-based chemotherapy has prognostic value. Based on this data, the Gynecological Cancer Intergroup (GCIG) Consensus defined 4 categories of subjects: 'platinum-sensitive,' progressing more than 12 months after the last chemotherapy; 'partially platinum-sensitive,' progressing between 6 and 12 months after the last chemotherapy; 'platinum-resistant,' progressing within 6 months of the last chemotherapy; and 'platinum-refractory,' progressing during or within 4 weeks of the last dose of chemotherapy (Friendlander et al 2011).

Most subjects with platinum-sensitive disease will respond further to platinum-based chemotherapy, and many will receive multiple lines of treatment over time but ultimately accumulate toxicities that limit the administration of further platinum-based therapy or develop platinum-based resistance. Subjects with platinum-resistant or refractory disease have generally poor prognoses and treatment options consist of non-platinum monotherapy including weekly paclitaxel, topotecan, PEGylated liposomal doxorubicin, and gemcitabine (Ledermann et al 2014). Following each subsequent relapse, subjects experience progressively shorter progression-free intervals and ultimately succumb to their disease (Colombo et al 2010).

In 2014, the US Food and Drug Administration (FDA) approved bevacizumab in combination with weekly paclitaxel, PEGylated liposomal doxorubicin, or topotecan for the treatment of subjects with platinum-resistant disease (Pujade-Lauraine et al 2014).

CCI [redacted]

BRCA and HRD

Numerous deoxyribonucleic acid (DNA) single-stranded breaks (SSBs) occur naturally as the result of normal metabolic activities and environmental factors, including ultraviolet light and radiation. Polyadenosine 5'diphosphoribose (poly [ADP ribose]) polymerase (PARP) plays an important role in identifying and repairing SSBs. PARP inhibition is an approach to targeting tumors with deficiencies in DNA repair mechanisms. PARP enzymes are essential for repairing DNA SSBs. Inhibiting PARPs leads to the persistence of SSBs, which are then converted to the more serious DNA double-stranded breaks (DSBs) during the process of DNA replication. Olaparib, through direct PARP enzyme inhibition and trapping of PARP with the DNA in an open configuration, prevents repair of SSBs. As cells undergo replication, SSBs are converted to harmful DSBs. In normal cells, DSBs are repaired by a DNA repair mechanism called homologous recombination repair (HRR). Cells with homologous recombination deficiency (HRD), resort to the more error prone repair mechanism called non-homologous end joining. In cells with HRD, DNA damage accumulates and leads to high genomic instability and eventual cell death. Cancer with HRD would thus be more sensitive to induction of cell death by PARP inhibitors (Farmer et al 2005, McCabe et al 2006).

The most common function-altering mutations associated with HRD are a mutation in the breast and ovarian cancer susceptibility genes *BRCA1* or *BRCA2*, which encode for 2 critical proteins in the homologous recombination repair pathway. *BRCA1* and *BRCA2* mutations that are defined as deleterious and suspected deleterious mutations are associated with loss-of-function of the protein.

BRCA1 and *BRCA2* defective tumors are intrinsically sensitive to PARP inhibitors, both in tumor models in vivo (Rottenberg et al 2008, Gelmon et al 2011, Hay et al 2009) and in the clinic (Fong et al 2009). The mechanism of action for olaparib is thought to result from the trapping of inactive PARP onto the SSBs, preventing their repair (Helleday 2011, Murai et al 2012). Olaparib, a PARP inhibitor, has been shown to inhibit selected tumor cell lines in vitro and in xenograft and primary explant models, as well as in genetic BRCA knock-out models, either as a stand-alone treatment or in combination with established chemotherapies.

Individuals with germline BRCA mutations (gBRCAms) will carry 1 mutant allele and 1 wild type allele, while their cancer cells would have lost the wild type copy of the BRCA gene. Normal cells in subjects who carry a gBRCAm can therefore repair DSBs with the functioning wild type BRCA allele. However, in cancer cells, the loss of heterozygosity leaves the non-functional germline BRCA (gBRCA) allele as the sole copy. In this way, PARP inhibition takes advantage of this difference and preferentially kills the cancer cells with minimal toxicity to normal cells (Rottenberg et al 2008, Gelmon et al 2011, Hay et al 2009).

Olaparib

The US FDA approved the tablet formulation of olaparib in August 2017.

The FDA approval of the tablet formulation is as follows:

- For the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, who are in complete or partial response to platinum-based chemotherapy.
- For the treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated advanced ovarian cancer who have been treated with 3 or more prior lines of chemotherapy. Patients for this indication are selected for therapy based on an FDA-approved companion diagnostic for olaparib.

The maintenance indication with the tablet formulation was based on 2 randomized, placebo-controlled, double-blind, multicenter studies in patients with recurrent ovarian cancer who were in response to platinum-based therapy.

SOLO-2 (NCT01874353) was a double-blind, placebo-controlled trial in which patients (N=295) with gBRCA-mutated ovarian, fallopian tube, or primary peritoneal cancer were randomized (2:1) to receive olaparib tablets 300 mg orally twice daily (*bid*) or placebo until unacceptable toxicity or PD. Randomization was stratified by response to last platinum chemotherapy (complete versus partial) and time to disease progression in the penultimate platinum-based chemotherapy prior to enrollment (6 months to 12 months versus > 12 months). All patients had received at least 2 prior platinum-containing regimens and were in response (complete or partial) to their most recent platinum-based regimen. All patients had a deleterious or suspected deleterious gBRCAm as detected either by a local test (n= 236) or central Myriad Clinical Laboratory Improvement Amendments test (n=59), subsequently confirmed by BRAC Analysis CDx (n= 286). The major efficacy outcome was investigator-assessed progression-free survival (PFS) evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Additional endpoints included overall survival (OS).

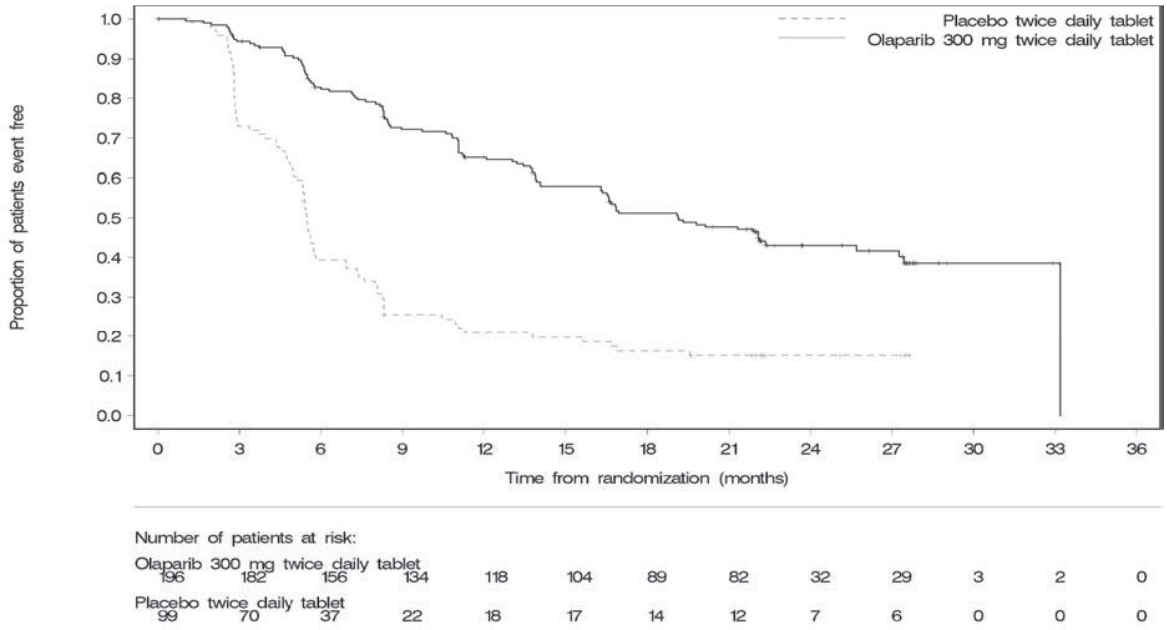
SOLO-2 demonstrated a statistically significant improvement in investigator-assessed PFS in patients randomized to olaparib as compared with placebo (Table 1 and Figure 1). Results from a blinded independent review were consistent. At the time of the analysis of PFS, OS data were not mature with 24% of events.

Table 1 Efficacy Results – SOLO-2 (Investigator Assessment)

	Olaparib tablets (n=196)	Placebo (n=99)
Progression-Free Survival		
Number of events (%)	107 (54.6%)	80 (80.8%)
Median, months	19.1	5.5
Hazard ratio[a] (95% confidence interval)	0.30 (0.22, 0.41)	
p-value[b]	<0.0001	

a Hazard ratio from the stratified proportional hazards model, stratified by response to last platinum chemotherapy (complete versus partial) and time to disease progression in the penultimate platinum-based chemotherapy prior to enrollment.
b The p-value is derived from a stratified log-rank test.
Source: SOLO-2

Figure 1 Kaplan-Meier Curves of Investigator-Assessed Progression-Free Survival – SOLO-2



Source: SOLO-2

Study 19 (NCT00753545) was a double-blind, placebo-controlled trial in which patients (N=265) with platinum-sensitive ovarian cancer who had received 2 or more previous platinum-containing regimens were randomized (1:1) to receive olaparib capsules 400 mg orally *bid* or placebo until unacceptable toxicity or PD. Randomization was stratified by

response to last platinum chemotherapy (CR versus PR), time to disease progression in the penultimate platinum-based chemotherapy (6 months to 12 months versus > 12 months), and descent (Jewish versus non-Jewish). The major efficacy outcome measure of the study was investigator-assessed PFS evaluated according to RECIST, v1.0.

The median age of patients treated with olaparib (n=136) was 58 years (range: 21 to 89) and 59 years (range: 33 to 84) among patients treated with placebo (n=129). Eastern Cooperative Oncology Group (ECOG) performance status was 0 in 81% of patients receiving olaparib and 74% of patients receiving placebo. Of all patients, 97% were White, 19% were enrolled in the US or Canada, 45% were in CR following their most recent platinum chemotherapy regimen, and 40% had a progression-free interval of 6 months to 12 months since their penultimate platinum. Prior bevacizumab therapy was reported for 13% of patients receiving olaparib and 16% of patients receiving placebo. A retrospective analysis for gBRCAm status, some performed using the Myriad test, indicated that 36% (n=96) of patients from the Intent-to-Treat population had deleterious gBRCAm, including 39% (n=53) of patients on olaparib and 33% (n=43) of patients on placebo.

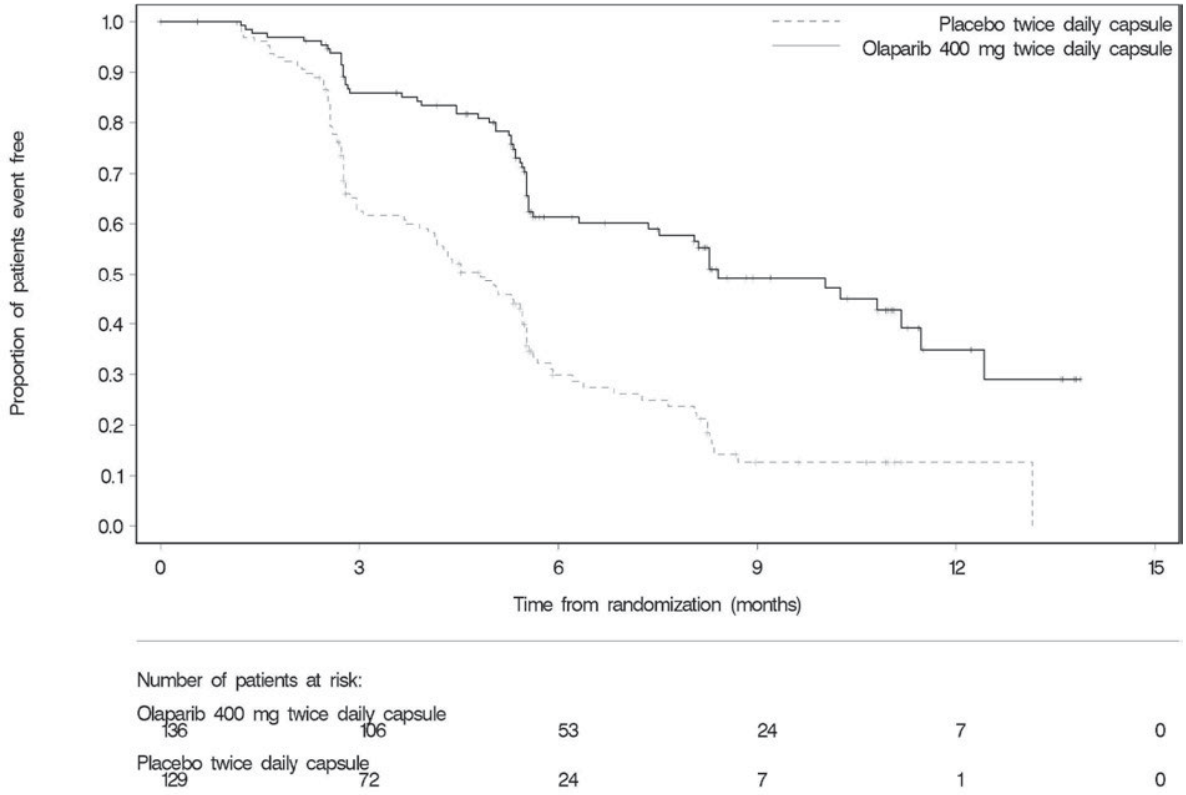
Study 19 demonstrated a statistically significant improvement in investigator-assessed PFS in patients treated with olaparib versus placebo (Table 2 and Figure 2).

Table 2 Efficacy Results – Study 19 (Investigator Assessment)

	Olaparib capsules (n=136)	**Placebo (n=129)**
Progression-Free Survival		
Number of events (%)	60 (44%)	94 (73%)
Median, months	8.4	4.8
Hazard ratio[a] (95% confidence interval)	0.35 (0.25, 0.49)	
p-value[b]	<0.0001	
Overall Survival[c]		
Number of events (%)	98 (72%)	112 (87%)
Median, months	29.8	27.8
Hazard ratio[a] (95% confidence interval)	0.73 (0.55, 0.95)	

a Hazard ratio from the stratified proportional hazards model, stratified by response to last platinum chemotherapy and time to disease progression in the penultimate platinum-based and Jewish and non-Jewish descent.
b The p-value is derived from a stratified log-rank test.
c Without adjusting for multiple analyses.
Source: Study 19

Figure 2 **Kaplan-Meier Curves of Investigator-Assessed Progression-Free Survival – Study 19**



Source: Study 19

The US FDA approved the capsule formulation of olaparib in December 2014 for monotherapy in subjects with deleterious or suspected deleterious gBRCAm (as detected by an FDA-approved test) advanced ovarian cancer who have been treated with 3 or more prior lines of chemotherapy.

This was based on Study 42 (Kaufman et al 2015) in which olaparib (400 mg *bid* 8 capsules) was given to 193 subjects in an advanced ovarian cancer cohort, of whom 178 had ovarian cancer, 4 had fallopian tube cancer, and 11 had primary peritoneal cancer; 148 (77%) of those in the ovarian cancer cohort had a germline mutation in *BRCA1*, 44 (23%) had a *BRCA2* mutation, and 1 had a germline mutation in both *BRCA1* and *BCRA2*. These subjects were heavily pretreated, with a mean number of 4.3 prior regimens. All subjects had received prior platinum therapy and were considered to be platinum-resistant or not suitable for further platinum therapy. The objective response rate (ORR) in this study was 31.1% (95% confidence interval [CI] = 24.6-38.1%), medium PFS was 7 months (54.6% progression-free at 6 months), and medium OS was 16.6 months (64.4% alive at 12 months).

In Study 20, a Phase II open-label, non-randomized study, women with advanced high-grade serous and/or undifferentiated ovarian carcinoma or triple-negative breast cancer received 400 mg olaparib capsules *bid*. Subjects were stratified according to whether they had a *BRCA1* or *BRCA2* mutation or not. Ninety-one subjects were enrolled (65 with ovarian cancer and 26 with breast cancer). In the ovarian cancer cohorts, confirmed objective responses were seen in 7 (41%; 95% CI = 22-64) of 17 subjects with *BRCA1* or *BRCA2* mutations and 11 (24%; 95% CI =14-38) of 46 patients without BRCA mutation (BRCAm) (Gelmon et al 2011).

In Study 19 (Ledermann et al 2014), olaparib (400 mg *bid* capsules) or matching placebo (randomized 1:1) was given as maintenance monotherapy to 265 subjects with platinum-sensitive relapsed high-grade serious ovarian cancer. In subjects with a BRCAm detected in their blood (gBRCAm) and/or tumor (somatic BRCA mutation [sBRCAm]), treatment with olaparib resulted in a significant increase in:

- PFS versus placebo (hazard ratio [HR] = 0.18; 95% CI = 0.10-0.31; $p < 0.0001$).

In subjects without a BRCAm (i.e., BRCA wild type [BRCAwt]), maintenance treatment resulted in a smaller, but still statistically significant increase in PFS (HR = 0.54; 95% CI = 0.34–0.85; p = 0.0075) (Ledermann et al 2014).

More recently, with longer follow-up from this study an OS clinical benefit for olaparib maintenance therapy in the overall and the BRCAm subject groups was observed (BRCAm OS HR = 0.62; 95% CI = 0.41-0.94; median 34.9 months olaparib, 30.2 months placebo) (Ledermann et al 2016).

Furthermore, clinical data in a small number of subjects within the sBRCAm subpopulation in Study 19 (Ledermann et al 2014) are consistent with the larger BRCA mutated dataset (gBRCA cohort), as fewer subjects on the olaparib arm reported progression events or death events. An exploratory analysis of tumor genetics in these subjects suggests that gBRCAm and sBRCAm in these tumors are indistinguishable in terms of their clonality and complete loss of the relevant BRCAwt allele.

To date, the sBRCAm olaparib data is available from these 20 sBRCAm subjects in Study 19. In Study 19 (Ledermann et al 2014), 10 subjects received olaparib and 10 subjects received placebo and were retrospectively assessed for PFS and OS. See Table 3 below.

Table 3 Progression and Death-Free Survival Events in sBRCAm Subjects in Study 19

Endpoint	Treatment	Events, n (%)
PFS	Olaparib 400 mg *bid* (n = 10) Placebo (n = 10)	3 (30.0) 8 (80.0)
Overall survival	Olaparib 400 mg *bid* (n = 10) Placebo (n = 10)	3 (30.0) 7 (70.0)
bid = twice daily; PFS = progression-free survival; sBRCAm = somatic BRCA mutation. Source: Dougherty et al 2015		

Hence, it is considered likely that olaparib may preferentially benefit subjects with sBRCAm tumors and subjects with loss-of-function mutations in other genes involved in the repair of double-stranded DNA breaks, i.e., those that are HRD and identified by a genetic scar (via Myriad's myChoice® HRD test) might benefit from olaparib and will be assessed further in this study.

Study tests

BRACAnalysis CDx®: The blood based BRACAnalysis CDx® test is the FDA-approved companion diagnostic test with olaparib for detection of gBRCA sequence variants. Subjects determined to carry a deleterious or suspected deleterious mutation in *BRCA1* or *BRCA2* can be considered to have a gBRCAm.

myChoice® HRD: The tumor based myChoice® HRD test simultaneously measures HRD through detection of 3 types of large rearrangements: loss of heterozygosity, telomeric allelic imbalance, and large-scale state transitions; and detects sequence variants in the *BRCA1* and *BRCA2* genes. Therefore, myChoice® HRD will inform on HRD and BRCA. An HRD score is used to assess a subject's level of deficiency in their tumor, and those carrying a deleterious or suspected deleterious mutation in *BRCA1* or *BRCA2* can be considered to have a tumor BRCAm.

Several research groups have used BRCAm ovarian and breast cancer as positive controls to develop such an assay (Abkevich et al 2012). This study will use the Myriad myChoice® HRD assay which was developed from the Abkevich et al approach as described by Timms et al 2014. The assay has been linked to sensitivity to platinum based chemotherapy and a similar assay was linked to response to another PARP inhibitor, but with a lower response rate than for BRCAm subjects (McNeish 2015).

myChoice® HRD is the first HRD test that can detect when a tumor has lost the ability to repair double-stranded DNA breaks, resulting in increased susceptibility to DNA-damaging drugs such as platinum drugs or PARP inhibitors. High myChoice® HRD scores reflective of DNA repair deficiencies are prevalent in all breast cancer subtypes, ovarian, and most other major cancers. In previously published data, Myriad showed that the myChoice® HRD test

predicted drug response to platinum therapy in certain subjects with triple-negative breast and ovarian cancers.

A study by Wilcoxen et al showed that the myChoice® HRD diagnostic test is predictive of BRCA deficiency and supports its use to help identify subjects with advanced ovarian cancer who may respond to treatment with niraparib, a PARP inhibitor. A total of 106 tumors from subjects with advanced ovarian cancer were evaluated for HRD and *BRCA1/2* mutations. The results showed that all BRCA deficient tumors (n = 26) were myChoice® HRD positive except 1. Additionally, the response to niraparib monotherapy was evaluated in 20 unique tumor models across a range of myChoice® HRD scores and all of the tumors that responded to niraparib were myChoice® HRD positive, irrespective of BRCA deficiency status (Wilcoxen et al 2015).

The double-blind, placebo-controlled, Phase III NOVA trial enrolled more than 500 subjects with recurrent ovarian cancer who were in a response to their most recent platinum-based chemotherapy. This trial demonstrated that niraparib significantly prolonged PFS compared to placebo control among subjects who were gBRCAm carriers (HR = 0.27, median PFS 21.0 months vs. 5.5 months, $p < 0.0001$). For subjects without a gBRCAm, but whose tumors were determined to be HRD positive using the Myriad myChoice® HRD test, niraparib significantly prolonged PFS (HR = 0.38, median PFS 12.9 months vs. 3.8 months, $p < 0.0001$). Niraparib also showed statistical significance in the overall non-gBRCAm cohort, which included subjects with both myChoice® HRD-positive and HRD-negative tumors (HR = 0.45, median PFS 9.3 months vs. 3.9 months $p < 0.0001$) (TESARO 2016).

In an exploratory analysis of olaparib from Study 19 (Ledermann et al 2014), there was some evidence suggesting that the HRD assay could identify BRCAwt subjects benefiting from olaparib maintenance therapy, although numbers were small (Hodgson et al 2015). Hence, there is a rationale and some supportive data to expect an increased PFS in this subject population, but with an expectation of a potentially lower effect size.

Subjects will be recruited to this study using 2 assays, BRACAnalysis CDx® (gBRCA status) and myChoice® HRD (tumor BRCA status and HRD status), running in parallel for cohort assignment.

Homologous recombination repair mutation (HRRm) gene panel: As a secondary objective, there will be a prospective baseline analysis using a test to assess germline mutations in a panel of genes from the HRR pathway. The panel is composed of 16 HRR pathway genes: *BRCA1*, *BRCA2*, ATM, RAD51B, RAD51C, RAD54L, RAD51D, FANC/BRIP1, FANCI, FANCL, FANCN(PALB2), BARD1, CHEK1, CHEK2, CDK12, and PPP2R2A. The result of this HRRm test will not determine cohort assignment, and will only be conducted in those subjects assigned to the cohorts with BRCAwt.

Indeed, deficiencies in the HRR pathway, such as those resulting from mutations in HRR genes, may confer sensitivity to PARP inhibitors (McCabe et al 2006).

As predicted by the biology, the somatic *BRCA1/2* mutations and mutations in 11 other HRR genes were reported to have a similar positive impact on OS and platinum responsiveness as germline *BRCA1/2* mutations (Pennington et al 2014). Study 19 also demonstrated that subjects with mutated HRR genes had benefits to their PFS (Hodgson et al 2015).

Exploratory analyses from the Study 19 (Ledermann et al 2014; Dougherty et al 2015) dataset showed that subjects with BRCAwt, but identified with HRD (either via myChoice® HRD or HRRm panel) derived benefit from olaparib therapy based on progression events (no ORR data available).

Table 4 Progression-Free Survival Hazard Ratio and 95% Confidence Interval by Cohort in Study 19

Subject Group	Number of subjects	PFS Hazard Ratio	95% CI
gBRCAm	95	0.17	0.09-0.31
gBRCAm + sBRCAm	135	0.18	0.10-0.31
gBRCAm + sBRCAm + myChoice® HRD positive	154	0.25	0.15-0.4
gBRCAm + sBRCAm + HRRm panel positive	157	0.2	0.12-0.33

CI = confidence interval; gBRCAm = germline BRCA mutation; HRD = homologous recombination deficiency; HRRm = homologous recombination repair mutation; PFS = progression-free survival; sBRCAm = somatic BRCA mutation.
Source: Ledermann et al 2014; Dougherty et al 2015

Although there is limited PFS data and a lack of ORR data available for subjects treated with olaparib that were characterized by these 2 HRD assays (myChoice® HRD and HRRm), and with albeit limited PFS data, these data provide some promising evidence to predict that olaparib could generate responses in each of these populations relating subjects with sBRCAm, HRRm, and HRD (genetic scar/myChoice® HRD) status to a clinical outcome (ORR).

1.2 Rationale for study design, doses, and control groups

The proposed Phase II study is designed to assess the benefit of olaparib tablets therapy in 4 cohorts of subjects with different statuses of BRCAms/HRD by assessing the efficacy (in the form of objective response) and safety of olaparib tablets monotherapy. This study will further assess the benefit of olaparib tablets in subjects beyond gBRCA, where limited evidence currently exists for benefit with the capsule formulation, i.e., in subjects with identified by myChoice® HRD (genetic scar) and HRRm (mutations in an identified panel of genes associated with HRR). Limited or no reported data exists for the tablet formulation in the second line treatment setting for olaparib and will be further assessed in these study populations.

Subjects will be enrolled into 1 of 4 cohorts based on gBRCA status and myChoice® HRD test with ORR as the primary endpoint. Homologous recombination repair mutation status relation to clinical outcome will be a secondary endpoint in this study and will be used to assess whether the gene panel additionally identified subjects who benefit from olaparib.

Secondary endpoints will also include duration of response (DoR), disease control rate (DCR), cancer antigen (CA)-125 response rate, PFS, time to any progression (TTAP, either CA-125 progression or objective progression or death), OS, mutation status of the HRRm related to clinical outcome, and safety assessments. Exploratory correlative studies will be conducted to assess potential biomarkers that correlate with clinical outcomes.

Platinum and taxane based chemotherapy is standard of care front-line treatment for women with ovarian cancer. Sixty to 90 percent of women will demonstrate an objective response to this therapy. (Markman et al 1991) The vast majority of these women will either have recurrence or progression of their disease. The choice of therapy at that time depends in part on platinum sensitivity. If a patient has platinum sensitive ovarian cancer they are generally retreated with a platinum regimen with responses of 17% to 79% (Gore et al 1990, Aghajanian et al 2012). The introduction of PARP inhibitors has provided an effective treatment option for women with ovarian cancer (Study 19 and SOLO-2). PARP inhibitors are being utilized for patients with fewer previous lines of therapy. The PARP inhibitor rucaparib was studied in relapsed, platinum-sensitive high-grade ovarian cancer in 204 evaluable patients, including 121 (59%) patients after 1 previous line of platinum-based chemotherapy (Swisher et al 2017). Results reported by Swisher et al were reported based on molecular profile, and not by line of therapy. Konecny (Konecny et al 2017) reported ORR in a subset of these patients treated with rucaparib: In 57 platinum-sensitive patients whose immediate prior therapy was platinum-based, the investigator-assessed ORR was 70% (95% CI: 57-72) for the overall population, with 83% , 86%, and 52% ORRs observed in patients treated with 1, 2, or 3 or more prior lines, respectively. PARP inhibitors in second-line therapy for recurrent ovarian cancer thereby have ORR similar to standard chemotherapy.

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1.3 Benefit/risk and ethical assessment

1.3.1 Unmet need

Ovarian cancer is a serious, life-threatening disease for which new medicines are needed. The current mainstay of therapy consists of multiple lines of chemotherapy, where a platinum agent is routinely employed. However, despite good initial responses in many platinum-sensitive subjects, the toxicity burden of platinum agents, including carboplatin is significant, with cumulative toxicity limiting the duration of treatment possible at each line of therapy. There is a large unmet need for a therapy that is well tolerated and can provide an alternative to chemotherapy for a well-defined subject population who have already received at least 1 prior platinum-based chemotherapy line.

Olaparib, a PARP inhibitor, is the first targeted agent to be approved for treatment in selected ovarian cancer subjects (gBRCAm). Potentially additional subjects beyond the gBRCA would benefit, including subjects with other types of detectable deficiencies in homologous DNA-damage repair. However, the biology of PARP would be expected to predict benefit in

BRCAm subjects, regardless of whether their mutation is detected by blood (germline) or tumor testing for BRCAm (Ledermann et al 2014) or other forms of HRD.

1.3.2 Clinical benefit

For specific information on the clinical benefit of olaparib monotherapy in subjects with platinum-sensitive relapsed gBRCAm ovarian cancer and in subjects without gBRCAm ovarian cancer, see the olaparib IB.

The FDA approval of the tablet formulation is as follows:

- For the maintenance treatment of adult patients with recurrent epithelial ovarian fallopian tube or primary peritoneal cancer, who are in complete response (CR) or partial response (PR) to platinum-based chemotherapy.
- For the treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated advanced ovarian cancer who have been treated with 3 or more prior lines of chemotherapy. Patients for this indication are selected for therapy based on an FDA-approved companion diagnostic for olaparib.

1.3.2.1 Clinical benefit of olaparib monotherapy in subjects with platinum-sensitive recurrent gBRCA mutated ovarian cancer

The pooled analysis from 6 olaparib (Phases I and II) monotherapy clinical studies consisting of 300 subjects with gBRCA mutated relapsed ovarian cancer (including fallopian tube and primary peritoneal), of whom 273 had measurable disease and were evaluable for response, demonstrated an ORR with olaparib in the overall group of 36% (97/273) and 7.4 months DoR (AstraZeneca data on file). The majority of the subjects (n = 223) had received 3 or more prior lines of therapy and of these, 205 subjects had measurable disease. In these subjects, the response rate was 31% (64/205) and DoR was 7.8 months. Nineteen percent (n = 51) of the 273 subjects with measurable disease were classified as platinum-sensitive. The response rate in the platinum-sensitive subjects was 53% (27/51) and the DoR was 8.2 months.

The majority of the subjects in the pooled analysis (n = 193) were enrolled in Study 42 (Domcheck et al 2016), a Phase II, open-label, non-randomized, non-comparative, multi-center study to assess the efficacy and safety of olaparib (400 mg capsules) given orally *bid* in subjects with advanced cancers, which were refractory to standard therapy or for whom no suitable, effective/curative therapy existed, and who had a confirmed genetic *BRCA1* and/or *BRCA2* mutation. In Study 42, there were 193 subjects with relapsed ovarian cancer (including fallopian tube and primary peritoneal), of whom 167 had measurable disease. In this overall group, the response rate was 36% (60/167) and DoR was 7.4 months (Kaufman et al 2015). Subjects were also analyzed by their platinum sensitivity status, if their last treatment was platinum based, and in the group of subjects who were classed as platinum-sensitive (when time from last platinum to PD was > 6 months) but ineligible to receive further platinum (typically due to hypersensitivity reactions), the response rate with

olaparib was higher than in the group of subjects with platinum-resistant disease (60% [15/25] vs. 15% [6/40], respectively) (Domcheck et al 2016).

Furthermore, 97 subjects in the pooled analysis were included from Study 12, a randomized, open-label, Phase II, dose-finding study of olaparib monotherapy (200 mg *bid* and 400 mg *bid* capsule) vs. PEGylated liposomal doxorubicin (PLD) in gBRCAm ovarian cancer subjects who had failed previous platinum therapy and were not considered candidates for further platinum treatment. The primary analysis of PFS (Investigator assessment) comparing both doses of olaparib to PLD did not demonstrate a statistically significant difference (n = 81; HR = 0.88; 95% CI = 0.51-1.56), median PFS 6.5 months, 8.8 months, and 7.1 months for the olaparib 200 mg, olaparib 400 mg, and PLD groups, respectively (Kaye S et al 2012). Objective response rates were 25%, 31%, and 18% for the olaparib 200 mg, 400 mg, and PLD groups, respectively. However, a pre-specified subgroup analysis in the platinum-sensitive subjects in the trial (n = 48), showed an HR for PFS numerically higher for the olaparib 400 mg group vs. PLD (n = 34; HR = 0.61; 95% CI = 0.24-1.50) with median PFS 9.2 months in the olaparib 400 mg group and 7.4 months in the PLD group and response rates of 47% and 26%, respectively.

In SOLO-2 investigator-assessed PFS (primary endpoint) was significantly longer for patients receiving olaparib versus placebo (HR = 0.30, 95% CI = 0.22-0.41, P<0.0001; median 19.1 months versus 5.5 months, respectively). The evaluation of PFS by blinded independent central review also demonstrated a significant PFS benefit in favor of olaparib (HR = 0.25, 95% CI = 0.18-0.35, P<0.0001; median 30.2 months versus 5.5months). The PFS benefit was supported by a significant improvement for olaparib in time to second progression (HR = 0.50, 95% CI = 0.34-0.72, P=0.0002), and a clinically meaningful improvement in time to first subsequent therapy or death (HR = 0.28, 95% CI = 0.21-0.38, P<0.0001) and time to second subsequent therapy or death (HR = 0.37, 95% CI = 0.26-0.53, P<0.0001). The OS data were immature at this data cut-off (maturity 24%) and median OS was not reached in either treatment group.

1.3.3 Safety and tolerability of olaparib

The tolerability profile of olaparib is characterized by clinical investigation and regulatory approval in 2014, including long term OS benefit (Ledermann et al 2016). It is suitable for long-term dosing until disease progression in subjects with relapsed platinum-sensitive ovarian cancer who carry a gBRCAm. For further information on the safety and tolerability of olaparib, including common adverse events, see the olaparib IB.

The most common adverse events considered to be associated with administration of olaparib include hematological effects (anemia, neutropenia, lymphopenia, thrombocytopenia, mean corpuscular volume elevation), decreased appetite, nausea and vomiting, diarrhea, dyspepsia, stomatitis, upper abdominal pain, dysgeusia, fatigue (including asthenia), increase in blood creatinine, headache, and dizziness. In a small number of subjects, pneumonitis, myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) and new primary malignancies have been reported. The cumulative incidences fall within that expected for the subject population under study in the reported literature. These events are considered potential

risks and are being closely monitored in ongoing studies. For further information on these important potential risks for olaparib, see the olaparib IB.

1.4 Study design

This Phase II, open-label, non-randomized, multi-center cohort study will assess the efficacy (ORRs) and safety of olaparib monotherapy in relapsed ovarian cancer subjects who have received at least 1 prior line of platinum-based chemotherapy and have measurable disease, who have progressed at least 6 months after their last platinum-based chemotherapy, and who either carry a germline deleterious or suspected deleterious BRCAm, have a BRCAm in their tumor, have an HRD tumor accessed via the myChoice® HRD tumor test, or have wild type tumor type (BRCA and HRD).

The primary endpoint of the study is ORR. Secondary endpoints will include DoR, CA-125 response rate, DCR, PFS, TTAP, OS, HRRm gene panel related to clinical outcome, and safety assessments. CCI

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Approximately 450 subjects will be screened to identify up to approximately 300 subjects to be enrolled in 4 cohorts which will include at least 30 subjects in each. An individual cohort may continue enrollment up to 90 subjects (unless early stopping criteria are met) at which point the cohort will be closed to further enrollment. Once all 4 cohorts have at least 30 subjects (unless early stopping criteria are met), the study will be closed to further enrollment. All subjects enrolled will receive olaparib tablets 300 mg CCI n the active treatment period of the study.

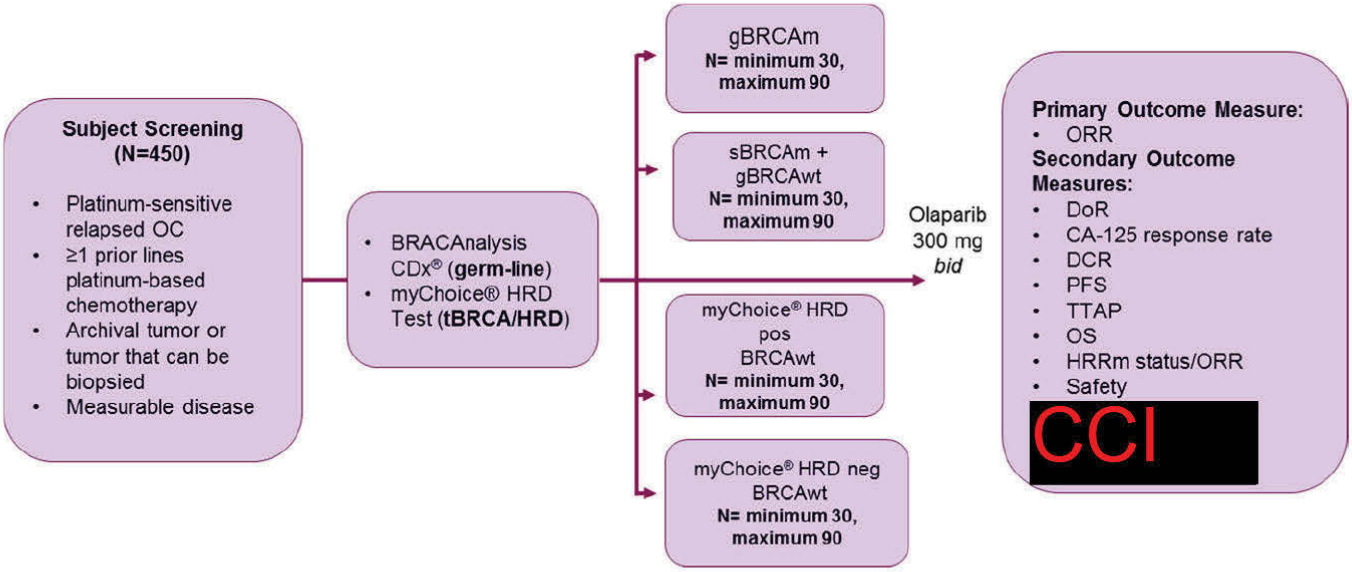
Subjects will continue treatment with olaparib tablets 300 mg CCI from enrollment (Visit 2) until objective radiological disease progression as per RECIST v1.1 as assessed by the Investigator, or when they meet any discontinuation criteria (see Section 3.9). After documentation of disease progression, subjects will be followed for survival.

All subjects who enrolled and received at least 1 dose of olaparib will be followed for survival. Subjects will be contacted to assess survival status every 12 weeks following disease progression until death, withdrawal of consent, or study closure. Survival information may be

obtained via telephone contact with the subject, subject's family, or by contact with the subject's current physician.

See Figure 3 for a diagram of the study.

Figure 3 Study Diagram



Bid = twice daily; BRCAwt = BRCA wild type; CA = Cancer antigen; DCR = disease control rate; DoR = duration of response; gBRCAm = germline BRCA mutation; gBRCAwt = germline BRCA wild type; HRD = homologous recombination deficiency; HRRm = homologous recombination repair mutation; neg = negative; OC = ovarian cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; pos = positive; RECIST = Response Evaluation Criteria in Solid Tumors; sBRCAm = somatic BRCA mutation.; tBRCA = tumor BRCA; TTAP = time to any progression (earliest of CA-125 progression, RECIST progression, or death).

2. STUDY OBJECTIVES

2.1 Primary objective

Primary Objective:	Outcome Measure:
To determine the clinical effectiveness of olaparib treatment in each of 4 cohorts assessed using ORR according to RECIST v1.1 criteria (Investigator determined).	• ORR, defined as the percentage of subjects with a best overall response of confirmed CR or PR (at any time up to and including the defined analysis cut-off point) divided by the number of subjects in the efficacy analysis set.

2.2 Secondary objectives

Secondary Objectives:	Outcome Measures:
To determine the clinical effectiveness of olaparib treatment in each of 4 cohorts assessed using: • DoR, • CA-125 response rate, • DCR, • PFS, • TTAP, • OS, and • HRRm gene panel status related to clinical outcome.	• DoR, for those subjects with a confirmed response of CR or PR, response duration will be measured from the date of the measurement criteria for CR or PR are first met until the date of documented objective progression or death in the absence of disease progression. • CA-125 response rate, defined as the percentage of subjects with a CA-125 response according to GCIG criteria divided by the number of subjects evaluable for CA-125 response. • DCR, defined as the percentage of subjects with a best overall response of confirmed CR or PR (at any time up to and including the defined analysis cut-off point) or who have demonstrated stable disease (SD) for at least 8 weeks from first dose, divided by the number of subjects in the efficacy analysis set. • PFS, defined as the time from the date of the first dose of olaparib to the earlier date of assessment of objective progression (per RECIST v1.1 criteria) or death by any cause in the absence of progression. • TTAP, defined as the time from the date of the first dose of olaparib to the earlier date of CA-125 progression (GCIG criteria) or RECIST v1.1 progression, or death by any cause in the absence of progression. • OS, defined as the time from the date of the first dose of olaparib to the date of death from any cause. • HRD status as per HRRm gene panel assessment (positive or negative) will be correlated with clinical outcome (ORR, defined above) for subjects enrolled in the 2 cohorts with BRCAwt (cohorts 3 and 4).

2.3 Safety objective

Safety Objective:	Outcome Measures:
To assess the safety and tolerability of single agent olaparib in each of 4 cohorts.	• Any adverse events, including serious adverse events (SAEs); physical examination; vital signs including blood pressure, pulse, and electrocardiogram (ECG); and collection of clinical chemistry/hematology parameters.

2.4 CCI

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3. SUBJECT SELECTION, ENROLLMENT, RESTRICTIONS, DISCONTINUATION, AND WITHDRAWAL

Each subject 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.

3.1 Inclusion criteria

For inclusion in the study, subjects must fulfill all of the criteria below.

1. Provision of written signed informed consent prior to any study specific procedures;

2. Subjects must be ≥ 18 years of age;

3. Female subjects with histologically diagnosed relapsed high-grade serous ovarian cancer (including primary peritoneal and/or fallopian tube cancer) or high-grade endometrioid cancer;

4. At least 1 lesion (measurable by RECIST v1.1) that can be accurately assessed at baseline by computed tomography (CT)/magnetic resonance imaging (MRI) and is suitable for repeated assessment;

5. Subjects must have received at least 1 prior platinum-based line of chemotherapy for ovarian cancer. Note: There is no limit on the number of lines of chemotherapy;

6. Subjects must be partially-platinum-sensitive (defined as progression 6 to 12 months after the end of the last platinum-based chemotherapy) or platinum-sensitive (defined as progression > 12 months after the end of the last platinum-based chemotherapy);

7. Subjects must have normal organ and bone marrow function measured within 28 days prior to administration of study treatment, as defined below:

   - Hemoglobin ≥ 9.0 g/dL with no blood transfusion in the past 28 days;
   - Absolute neutrophil count (ANC) ≥ 1.5×10^9/L;
   - Platelet count ≥ 100×10^9/L;
   - Total bilirubin (TBL) ≤ 1.5 × institutional upper limit of normal (ULN);
   - Aspartate aminotransferase (AST) (serum glutamic oxaloacetic transaminase/alanine aminotransferase (ALT) (serum glutamic pyruvate transaminase ≤ 3 × institutional ULN, unless liver metastases are present in which case they must be ≤ 5 × ULN); and
   - Subjects must have serum creatinine ≤ 1.5 × ULN, OR creatinine clearance estimated using the Cockcroft-Gault equation of ≥ 51 mL/min (below). Subjects with severe renal impairment (CrCl ≤ 30 mL/min) are excluded, regardless of measured serum creatinine.

$$\text{Estimated creatinine clearance} = \frac{(140\text{-age [years]}) \times \text{weight (kg)}}{\text{serum creatinine (mg/dL)} \times 72} \quad (\times 0.85)^{a}$$

[a] for all female subjects in the study

8. ECOG performance status 0 to 1 (see Appendix F);

9. Subjects must have a life expectancy ≥ 16 weeks;

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

    - Postmenopausal is defined as:

    – Amenorrheic for 1 year or more following cessation of exogenous hormonal treatments,

    – Luteinizing hormone and follicle stimulating hormone levels in the post-menopausal range for women under 50,

    – Radiation-induced oophorectomy with last menses > 1 year ago,

    – Chemotherapy-induced menopause with > 1 year interval since last menses, or

    – Surgical sterilization (bilateral oophorectomy or hysterectomy);

    - Female subjects who are of childbearing potential, who are sexually active, must agree to the use of 2 highly effective forms of contraception in combination (see Appendix E for acceptable methods) from the signing of the informed consent and throughout the period of taking study treatment and for 1 month after the last dose of study medication, or they must totally/truly abstain from any form of sexual intercourse;

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

12. Formalin fixed, paraffin embedded tumor sample (either archival or fresh sample) from the primary or recurrent cancer **must** be available for central testing. If there is not written confirmation of the availability of an archived or fresh tumor sample prior to enrollment, the subject is **not** eligible for the study.

3.2 Exclusion criteria

For inclusion in the study, subjects cannot 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 Representative staff and/or staff at the study site);

2. Previous enrollment in the present study;

3. Exposure to any investigational product (IP) within 30 days or 5 half-lives (whichever is longer) prior to start of study treatment;

4. Any previous treatment with a PARP inhibitor, including olaparib;

5. Subjects who have platinum-resistant or refractory disease defined as progression during or within 6 months of the last platinum-based chemotherapy;

6. Other malignancy within the last 5 years except: adequately treated non-melanoma skin cancer; curatively treated in situ cancer of the cervix; ductal carcinoma in situ; Stage 1, grade 1 endometrial carcinoma; or other solid tumors including lymphomas (without bone marrow involvement) curatively treated with no evidence of disease for ≥ 5 years. Subjects with a history of localized triple negative breast cancer may be eligible, provided they completed their adjuvant chemotherapy more than 3 years prior to registration, and that the subject remains free of recurrent or metastatic disease;

7. Resting ECG with clinically significant abnormal findings;

8. Subjects receiving any systemic chemotherapy or radiotherapy (except for palliative reasons) within 3 weeks prior to study treatment;

9. Concomitant use of known strong CYP3A inhibitors (e.g., itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (e.g., ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil). The required washout period prior to starting olaparib is 2 weeks;

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

11. Persistent toxicities (> Common Terminology Criteria for Adverse Event [CTCAE] grade 2) caused by previous cancer therapy, excluding alopecia;

12. Subjects with MDS/AML or with features suggestive of MDS/AML;

13. Subjects with pneumonitis or at risk of pneumonitis;

14. Subjects with symptomatic uncontrolled brain metastases. No stereotactic radiation or whole brain radiation within 28 days prior to Cycle 1, Day 1. A scan to confirm the absence of brain metastases is not required. The subject can receive a stable dose of corticosteroids before and during the study as long as these were started at least 4 weeks prior to treatment. Subjects with spinal cord compression, unless considered to have received definitive treatment for this and with evidence of clinically stable disease for 28 days;

15. Major surgery within 2 weeks of starting study treatment, and subjects must have recovered from any effects of any major surgery;

16. Subjects considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease, or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, extensive interstitial bilateral lung disease on High Resolution CT scan, or any psychiatric disorder that prohibits obtaining informed consent;

17. Subjects unable to swallow orally administered medication, and subjects with gastrointestinal disorders likely to interfere with absorption of the study medication;

18. Breastfeeding women;

19. Immunocompromised subjects, e.g., subjects who are known to be serologically positive for human immunodeficiency virus;

20. Subjects with a known hypersensitivity to olaparib or any of the excipients of the product;

21. Subjects with known active hepatitis (i.e., Hepatitis B or C) due to risk of transmitting the infection through blood or other body fluids;

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

23. Whole blood transfusions in the last 120 days prior to entry into the study (packed red blood cells and platelet transfusions are acceptable; for timing refer to inclusion criterion number 7 [No blood transfusion can have occurred in the past 28 days]).

For procedures for withdrawal of incorrectly enrolled subjects, see Section 3.4.

3.3 Subject enrollment

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

The Investigator(s) will:

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

2. Assign the potential subject a unique enrollment number, beginning with ‘E#’; and

3. Determine subject eligibility. See Section 3.

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

3.4 Procedures for handling incorrectly enrolled subjects

Subjects who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Subjects who are enrolled but subsequently are found not to meet all of the eligibility criteria must not be initiated on treatment and must be withdrawn from the study (see Section 3.10).

Where a subject does not meet all of the eligibility criteria but is incorrectly started on treatment, the Investigator should inform the AstraZeneca Representative Study Physician immediately, and a discussion should occur between the AstraZeneca Representative Study Physician and the Investigator regarding whether to continue or discontinue the subject from treatment. The AstraZeneca Representative Study Physician must ensure all decisions are appropriately documented.

3.5 Methods for assigning cohorts

Eligible subjects will be enrolled into 1 of 4 cohorts based upon genetic testing performed by a central laboratory to achieve at least 30 subjects in each cohort:

- Cohort 1: gBRCAm,
- Cohort 2: sBRCAm and germline BRCA wild type,
- Cohort 3: myChoice® HRD positive (genomic instability positive) and BRCAwt (no BRCA mutation), or
- Cohort 4: myChoice® HRD negative (genomic instability negative) and BRCAwt (no BRCA mutation).

Cohort enrollment rules:

The objective response will be monitored on an ongoing basis for subjects in each cohort. If no responses (CR or PR) are observed in the first 15 subjects in a cohort, in consultation with the Steering Committee, this cohort will be closed to further enrollment. However, if there is at least 1 confirmed objective response in the first 15 subjects, that would justify continuing enrollment up to a maximum of 90 subjects. This stopping rule applies to all cohorts. Enrollment in each cohort will continue while the objective response is being assessed for the futility assessment. The objective response will be assessed as per protocol, i.e., allowing 6 months of follow up.

All eligible subjects will provide a screening blood sample for the Myriad BRACAnalysis CDx® analysis and a screening tumor sample for the myChoice® HRD analysis. Investigative sites will ship these samples to the central laboratory directly. The testing results will be provided back to the Investigator within approximately 14 to 21 days. The Myriad testing may be submitted in advance of the 28-day screening window if the subject consents to the appropriate pre-screening informed consent form.

Prior to any cohorts being closed to enrollment, subjects may enroll in the study and initiate treatment prior to the Myriad BRACAnalysis CDx® and myChoice® HRD tests being reported; however, subjects will not be allocated into a cohort until the results are received by the Investigator. Once the test results are received by the Investigator, the subject will be allocated into the appropriate cohort. Once a cohort reaches 90 subjects, the cohort will be closed, and subjects may not initiate treatment until their Myriad BRACAnalysis CDx® and myChoice® HRD tests are completed, the results are received by the Investigator, and it is confirmed there is an open cohort available for which the subject is eligible.

Any subject with a known BRCAm status is still required to have her BRCAm status confirmed using the Myriad BRCAnalysis CDx® test (gBRCA) or myChoice® HRD test (sBRCA).

Once the results are received by the Investigator, the subject's cohort assignment will be determined and recorded in the study's electronic data capture (EDC) system.

3.6 Methods for ensuring blinding (Not applicable)

3.7 Methods for unblinding (Not applicable)

3.8 Restrictions

For a listing of concomitant medications see Section 7.7.

3.8.1 Grapefruit juice

The subject must not consume grapefruit juice while on olaparib therapy.

3.8.2 Contraception

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

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

3.8.3 Breastfeeding/lactation

Women are not permitted to breastfeed during this study. Lactating women can be eligible if they stop breastfeeding prior to the first dose of the study drug until at least 30 days after the last dose of the study drug.

3.9 Discontinuation of investigational product

Subjects may be discontinued from olaparib in the following situations:

- Subject decision. The subject is at any time free to discontinue treatment, without prejudice to further treatment;
- Adverse event;
- Severe non-compliance with the Clinical Study Protocol;
- Investigator determines it is in the best interest of the subject to discontinue study treatment;
- Bone marrow findings consistent with MDS/AML; or
- Objective progression according to RECIST v1.1 criteria.

3.9.1 Procedures for discontinuation of a subject from investigational product

At any time, subjects are free to discontinue olaparib or withdraw from the active treatment phase of the study (i.e., olaparib and assessments – see Section 3.10), without prejudice to further treatment. A subject who decides to discontinue olaparib will complete the Study Treatment Discontinuation Visit (see Section 4.2.5) and will be asked about the reason(s) for discontinuation and the presence of any adverse events. Adverse events will be followed-up (see Section 6), and all study medications should be returned by the subject.

By discontinuing from study treatment, the subject then enters the survival follow-up phase of the study. Subjects should be followed for progression (if discontinuation in the absence of progression) and survival following treatment discontinuation as per the study plan (see Section 4.3 and Table 6). Any subject who has not yet shown objective radiological disease progression at withdrawal from olaparib should continue to be followed as per RECIST v1.1.

Any subject discontinuing olaparib should be seen at 30 days post-discontinuation for the evaluations outlined in the study plan. The subject's tumor status should be assessed clinically, and, if appropriate, disease progression should be confirmed by radiological assessment via RECIST v1.1 criteria. After discontinuation of study medication, the Principal Investigator/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 subject. In addition, they will record in the electronic case report form (eCRF) the date of discontinuation, the reasons, manifestation, and treatment at the time of discontinuation. If a subject discontinues study treatment, the AstraZeneca Representative Study Physician must be informed immediately. The Subject will be required to attend the treatment discontinuation visit.

After discontinuation of the study medication at any point in the study, all ongoing adverse events or SAEs must be followed until resolution unless, in the Investigator's opinion, the condition is unlikely to resolve due to the subject's underlying disease, or the subject is lost to

follow-up (see Section 6.3.2). All new adverse events and SAEs occurring during the 30 calendar days after the last dose of study medication must be reported (if SAEs, they must be reported to AstraZeneca Safety representative **within 24 hours** as described in Section 6.4) and followed to resolution as above. Subjects should be seen at least 30 days after discontinuing study medication to collect and/or complete adverse event information. For guidance on reporting adverse events after the 30 day follow-up period see Section 6.3.1.1.

All subjects who received at least 1 dose of olaparib must be followed for progression and survival through the final analysis of all primary and secondary endpoints (approximately 6 months after the last subject has commenced study treatment [received at least 1 dose of olaparib]) + an additional 12 months after the data cut-off for follow-up for survival for applicable subjects. At the end of this additional 12 months of survival follow-up, updated OS and safety analyses will be conducted and the study will be closed. Subjects are, however, permitted to continue to receive olaparib beyond the closure of the database if, in the opinion of the Investigator, they are continuing to receive benefit from treatment with olaparib. During this time, adverse events of special interest and SAEs must still be collected and reported until 30 days after the subject finally stops taking olaparib. See Section 4.3.

If a subject is withdrawn from the study, see Section 3.10. See Section 3.10.2 for details on subject replacement.

For information regarding the withdrawal of consent for donated biological samples, see Section 5.6.9.

3.10 Criteria for withdrawal

Reasons for withdrawal from the study:

- Voluntary withdrawal by the subject who is at any time free to discontinue their participation in the study, without prejudice to further treatment (see Section 3.10.2);
- Incorrectly enrolled subjects (i.e., the subject does not meet the required inclusion/exclusion criteria for the study) (see Section 3.4);
- Subject lost to follow-up; or
- Death.

3.10.1 Screen failures

Screening failures are subjects who have signed informed consent and do not fulfill the eligibility criteria for the study, and therefore must not be enrolled.

3.10.1.1 Laboratory re-screening

If a subject is determined to be a screen failure on the basis of a laboratory results, during the screening period (28 days), the laboratory value may be rechecked to determine if the value

has changed to make the subject eligible. However, the 28-day screening period will not be extended.

3.10.2 Withdrawal of the informed consent

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

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

If a subject withdraws from participation in the study, her enrollment code cannot be reused. Withdrawn subjects will be replaced if the subject is withdrawn prior to the first post-baseline objective response assessment. Withdrawn subjects will not be replaced if the subject has had a post-baseline objective response assessment.

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

- Further participation in the study including any further survival follow-up (e.g., survival calls);
- Withdrawal of consent to the use of their study generated data; or
- Withdrawal to the use of any samples (see Section 5.6.9).

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

For information regarding the withdrawal of consent for donated biological samples, see Section 5.6.9.

3.11 Discontinuation of the study

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

- Meet individual stopping criteria or are otherwise considered significant;
- Are assessed as causally related to study medication; or
- Are not considered to be consistent with continuation of the study.

Regardless of the reason for study termination, all data available for the subject at the time of study discontinuation must be recorded in the eCRFs.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the subjects' interests. See Section 9.3 for timelines for planned study completion.

4. STUDY PLAN AND TIMING OF PROCEDURES

This is a Phase II, open-label, non-randomized, multi-center cohort study assessing the efficacy and safety of olaparib tablets 300 mg CCI in subjects with platinum-sensitive or partially platinum-sensitive, relapsed, high-grade serous or high-grade endometrioid ovarian, fallopian tube, or primary peritoneal cancer, who have received at least 1 prior line of platinum-based chemotherapy.

The study will assess the effectiveness of olaparib tablets as measured by the ORRs as determined by RECIST v1.1, in subjects with gBRCAm, sBRCAm, or potential aberrations in HRD as determined by myChoice® HRD, as well as in subjects without identifiable HRD. This study will utilize Myriad BRACAnalysis CDx® for germline BRCA analysis and a tumor test (myChoice® HRD) for tumor BRCA analysis and HRD status. The Myriad testing may be submitted in advance of the 28-day screening window if the subject consents to the appropriate pre-screening informed consent form.

Four cohorts will be identified based upon genetic testing:

- Cohort 1: gBRCAm,
- Cohort 2: somatic BRCA mutated (sBRCAm) and germline BRCA wild type,
- Cohort 3: myChoice® HRD positive (genomic instability positive) and BRCA wild type (BRCAwt) (no BRCA mutation),
- Cohort 4: myChoice® HRD negative (genomic instability negative) and BRCAwt (no BRCA mutation).

For the cohort enrollment stopping rules, see Section 3.5 and Section 8.5.4.

This study consists of an up to 28-day screening period (Day -28 to Day -1) once the subject signs the main study consent. See Section 4.1.

Following the screening period, eligible subjects will enter the active treatment period of the study. Study visits will be conducted at Day 1 (Visit 2), Day 8 (Visit 3), Day 15 (Visit 4), Day 22 (Visit 5), Day 29 (Visit 6), and on Day 1 of a 4-week visit period up to 52 weeks (if not progressed and still on treatment), then on Day 1 of a 12-week visit period relative to date

of enrollment. For a list of specific procedures and assessments conducted during the active treatment period, see Section 4.2. When the subject discontinues olaparib, the Study Treatment Discontinuation Visit will be conducted (see Section 4.2.5).

Subjects should be discontinued from active study treatment phase if they have objective radiological disease progression according to RECIST v1.1 (see Appendix G) and complete the Study Treatment Discontinuation Visit as per the study plan.

A data cut-off for analysis of all primary and secondary endpoints will occur approximately 6 months after the last subject enrolled has commenced study treatment (received at least 1 dose of olaparib). The study will remain open for an additional 12 months after this data cut-off for survival follow-up for applicable subjects. At the end of this additional 12 months of survival follow-up, updated OS and safety analyses will be conducted and the study will be closed. Subjects are, however, permitted to continue to receive olaparib beyond the closure of the database if, in the opinion of the Investigator, they are continuing to receive benefit from treatment with olaparib. During this time, adverse events of special interest and SAEs must still be collected and reported until 30 days after the subject finally stops taking olaparib. See Section 4.3.2.

Assessments for survival will be made every 12 weeks (± 1 week) following objective radiological disease progression (RECIST v1.1). See Section 4.4.

A Follow-up Visit will be conducted 30 days after the discontinuation of olaparib (see Section 4.3.1).

Table 6 Study Plan – On Study Treatment and Discontinuation

Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**Subsequent on treatment visits every 4 weeks [a] Tumor assessment visits every 8 or 12 weeks [b] Visit No. 7 onwards**	**Study treatment discontinued [c]**	**Follow-up 30 days after last dose of study medication [d]**	**Overall Survival Follow-up [e]**
Day	-28 to -1	1	8	15	22	29	Day 1 of next visit period [f]			
Visit Window			± 3d	± 3d	± 3d	± 3d	± 3d	+ 7d	± 7d	± 7d
Informed consent [g]	X									
Demographics	X									
Surgical and medical history	X									
Prior cancer therapies including radiotherapy	X									
Inclusion/exclusion criteria (history of blood transfusions) [h]	X									
Enrollment		X								
Physical examination [i]	X	X						X		
Vital signs, body weight, height, (Includes BP, pulse, and temperature), and ECG [i, j]	X	X							X	
ECOG performance status	X	X					X	X		
Hematology/clinical chemistry [k]	X	X	X	X	X	X	X	X	X	
Urinalysis	X									

Table 6 Study Plan – On Study Treatment and Discontinuation

Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**Subsequent on treatment visits every 4 weeks [a]** **Tumor assessment visits every 8 or 12 weeks [b]** **Visit No. 7 onwards**	**Study treatment discontinued [c]**	**Follow-up 30 days after last dose of study medication [d]**	**Overall Survival Follow-up [e]**
Day	-28 to -1	1	8	15	22	29	Day 1 of next visit period [f]			
Visit Window			± 3d	± 3d	± 3d	± 3d	± 3d	+ 7d	± 7d	± 7d
Pregnancy test [l]	X	X				X	X		X	
Blood sample for determination of *BRCA* status via Myriad [m,n]	X									
Blood sample for disease specific marker (CA-125) [o]		X				X	X	X		
Tumor Assessment (CT or MRI according to RECIST v1.1)	X [p]	Every 8 weeks (± 1 week) from receipt of first dose of study drug (Visit 2) for 48 weeks and every 12 weeks (± 1 week) thereafter until PD has been determined by the Investigator according to RECIST v1.1 criteria (including confirmatory RECIST scan).								
Adverse events (continuous from the time of informed consent) [q]	X	X	X	X	X	X	X	X	X	
Concomitant medications including blood transfusions	X	X	X	X	X	X	X	X	X	
Olaparib dispensed/returned [r]		X				X	X	X		

Table 6 Study Plan – On Study Treatment and Discontinuation

Visit Number	1	2	3	4	5	6	Subsequent on treatment visits every 4 weeks [a] Tumor assessment visits every 8 or 12 weeks [b] Visit No. 7 onwards	Study treatment discontinued [c]	Follow-up 30 days after last dose of study medication [d]	Overall Survival Follow-up [e]
Day	-28 to -1	1	8	15	22	29	Day 1 of next visit period [f]			
Visit Window			± 3d	± 3d	± 3d	± 3d	± 3d	+ 7d	± 7d	± 7d
Subsequent cancer therapy following discontinuation of study treatment [s]									X	
Blood sample for pharmacogenetics (mandatory) [t]		X								
Tumor sample (mandatory) [m, n,u,v]	X									
CCI [redacted]								[redacted]		
[redacted]		[redacted]						[redacted]		
[redacted]		[redacted]						[redacted]		
[redacted]										X

a. Visit to take place on Day 1 of a 4-week visit period up to 52 weeks (if not progressed and still on treatment), then on Day 1 of a 12-week visit period relative to date of enrollment until PD (RECIST v1.1).

b. Follow-up assessments will be performed at the end of every 8 weeks (± 1 week) up to 48 weeks, then every 12 weeks (± 1 week) relative to date of enrollment until PD (RECIST v1.1). Follow-up CT or MRI assessments (per RECIST v1.1) will be by chest (in those subjects 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. Subjects must be followed until RECIST PD. If an unscheduled assessment was performed and the subject has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits. Subjects who are determined to have PD according to RECIST v1.1 criteria (including confirmatory RECIST scan) by the Investigator may have additional scans performed per the site's standard of care. Scans will be collected through disease progression.

c. Subjects should be discontinued from study treatment if they have objective radiological disease progression according to RECIST v1.1 (see Appendix G) and complete the Study Treatment Discontinuation Visit as per the study plan.
d. During the follow-up period, subjects will be followed for PFS (CA-125 and radiographic evidence of progression per site standards) until database lock/end of study, and assessed for overall survival.
e. Assessments for survival should be made every 12 weeks (± 1 week) following disease progression. Survival information may be obtained via telephone or email contact with the subject, subject's family, or by contact with the subject's current physician.
f. Visit 7 equals Day 57 (Week 8), then Visit 8 equals Day 85 (Week 12), etc.
g. Informed consent for pre-screening will be taken specifically for myChoice® HRD (central Myriad HRD tumor) and BRACAnalysis CDx® (gBRCA testing). A separate informed consent needs to be signed to begin study procedures for the overall study.
h. All inclusion/exclusion criteria including history of blood transfusion within previous 120 days from informed consent and the reasons (e.g., bleeding or myelosuppression).
i. Height will only be recorded at screening. Temperature and weight only required if clinically indicated. Physical examination should be performed according to the schedule; after the baseline assessment it is not necessary to record the details on an eCRF unless related to an adverse event/SAE. Any clinically significant changes should be recorded as adverse events.
j. The ECG at screening should be performed within 7 days prior to starting the study treatment. Electrocardiograms should be performed once the subject has been in the supine position for at least 5 minutes in each case.
k. Coagulation tests are only required if clinically indicated. For a list of all required laboratory tests, please refer to Section 5.2.1. All enrolled subjects will have safety blood samples taken weekly during the first month on treatment followed by monthly assessments until discontinuation of study treatment. Safety blood samples will be taken at the 30-day Follow-up Visit as well.
l. Women of childbearing potential must have a negative urine or serum pregnancy test within 28 days prior to starting treatment and a confirmatory test on Day 1 before initiating olaparib treatment; and at the timepoints shown in Table 6 during study treatment, and at the 30 day follow up visit. Pregnancy testing for women of childbearing potential should be conducted at regular intervals (eg, monthly). If results are positive, the subject is ineligible/must be discontinued from the study.
m. Subjects with an unknown gBRCA status will have their blood and tumor tested with the myChoice® HRD and BRACAnalysis CDx® in parallel at pre-screening (if consented) or at screening, if not previously performed by Myriad during pre-screening.
n. Subjects with known gBRCA status from the local laboratory must provide a blood and tumor sample at screening for confirmatory purposes. Their involvement in the study will not be affected by the result of the Myriad test.
o. CA-125 will be tested at baseline and every month thereafter until objective disease progression, based on progressive serial elevation of serum CA-125 according to the modified GCIG criteria. Samples should be taken pre-dose at Visit 2.
p. RECIST assessments will be performed using CT/MRI of the chest, abdomen, and pelvis, with other regions as clinically indicated for the assessment of disease, no more than 28 days prior to study treatment start and as close as possible to the start of study treatment. A CT examination with intravenous contrast media administration is the preferred method. An MRI should be used where CT is not feasible or it is medically contraindicated.

q. When an adverse event for nausea and vomiting occurs, an additional eCRF will require completion. All ongoing adverse events/SAEs and any new adverse events/SAEs identified during the 30 calendar day follow-up period after last dose of study medication must be followed to resolution (or stabilization or return to baseline). A targeted questionnaire will be sent to any Investigator reporting an AESI as an aid to provide further detailed information on the event.

r. Sufficient olaparib should be dispensed for at least each active treatment period plus overage; however, additional treatment can be dispensed to subjects to last longer in accordance with local practice.

s. All anti-cancer treatments (including, but not limited to, chemotherapy and targeted agents), and the Investigator's opinion of response to them plus the date of progression, post-discontinuation of study treatment, need to be recorded.

t. Only 1 sample should be collected per subject for pharmacogenetics during the study. The sample should be taken pre-dose.

u. Subjects must provide a tumor sample to be considered for the study – the sample can either be an archival sample or a new baseline tumor sample. If a tumor sample is taken at pre-screening for Myriad testing a sample will not need to be re-taken for Myriad testing; independent of the tumor sample for Myriad testing, an additional sample must be provided at screening for future research purposes.

v. The biopsied tumor should not be assessed as a target lesion as part of the RECIST assessments if there are other lesions available. The biopsy should be taken after the baseline scan has been performed.

w. CCI [redacted]

[redacted] CCI [redacted]

[redacted]

AESI = adverse event of special interest; BP = blood pressure; CA = Cancer antigen; CT = computed tomography; CCI [redacted] CCI [redacted] ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; gBRCA = germline BRCA; GCIG = Gynecological Cancer Intergroup; HRD = homologous recombination deficiency; MRI = magnetic resonance imaging; No. = number; PD = progressive disease; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event.

4.1 Enrollment/screening period

Procedures will be performed according to the Study Plan, Table 6.

During screening, consenting subjects are assessed to ensure that they meet study eligibility criteria per Section 3. Subjects who do not meet these criteria must not be enrolled in the study.

Subjects will be considered enrolled once the subject has signed the Informed Consent Form (full study) and has met all inclusion and none of the exclusion criteria. Note: Prior to any cohort being filled, subjects can initiate study drug treatment prior to cohort assignment. Once a cohort has been closed to further enrollment, subjects may not initiate treatment until the Myriad BRACAnalysis CDx® and myChoice® HRD testing demonstrates the subject is eligible for an open cohort, at which point the subject may initiate study drug. If the results demonstrate the subject was eligible for a closed cohort, the subject will be discontinued from the study. See Section 3.5 for information about cohort assignment.

The following procedures can be performed at pre-screening if the subject has consented to pre-screening:

- Obtain informed consent specifically for central Myriad HRD tumor (myChoice® HRD) and gBRCA testing (BRACAnalysis CDx®);
- Obtain blood sample for determination/confirmation of BRCA status via Myriad BRACAnalysis CDx® (see Table 8); and
- Obtain archival tumor sample and/or baseline tumor sample for Myriad testing; subjects must provide a tumor sample to be considered for the study – the sample can either be an archival sample or a new baseline tumor sample (see Section 5.6);

The following procedures will be performed at screening (Day -28 to Day -1):

- Obtain informed consent specifically for central Myriad HRD tumor (myChoice® HRD) and gBRCA testing (BRACAnalysis CDx®) if not previously obtained through pre-screening consent;
- Obtain informed consent for overall study; and
- Confirm eligibility based on all inclusion/exclusion criteria (see Sections 3.1 and 3.2);

– Obtain demographics and medical and surgical history;

– Obtain prior cancer therapies, including radiotherapy;

- Obtain blood sample for determination/confirmation of BRCA status via Myriad BRACAnalysis CDx® (see Table 8) if not previously obtained for Myriad testing;
- Obtain archival tumor sample and/or baseline tumor sample(s); subjects must provide a tumor sample to be considered for the study – the sample can either be an archival sample or a new baseline tumor sample (see Section 5.6); Note: The tumor sample for Myriad HRD testing should only be taken if not previously obtained through pre-screening. CCI [redacted] CCI .
- Assess functional status using the ECOG performance status scale (see Appendix F);
- Perform physical examination (see Section 5.2.2);
- Obtain vital signs, body weight, and body height (see Section 5.2.4);
- Obtain ECG (see Section 5.2.3);
- Obtain sample for hematology and clinical chemistry (see Section 5.2.1 and Table 8);
- Obtain sample for urinalysis (see Section 5.2.1 and Table 7);
- Obtain sample for pregnancy test, if necessary (see Section 5.2.5.1);
- Assess tumor (CT or MRI according to RECIST v1.1) (see Section 5.1.1);
- Assess and record concomitant medications (including blood transfusions); and
- Assess subject for adverse events (continuous from time of informed consent).

4.2 Treatment period

Descriptions of the procedures for this period are included in the Study Plan, Table 6.

4.2.1 Study Visit 2, Day 1

The following procedures will be performed at Visit 2, Day 1:

- Obtain sample for pregnancy test, if necessary (see Section 5.2.5.1);
- Enroll subject;

- Perform physical examination (see Section 5.2.2);
- Obtain vital signs, body weight, and ECG (see Sections 5.2.3 and 5.2.4);
- Assess functional status using the ECOG performance status scale (see Appendix F);
- Obtain pre-dose blood sample for hematology/clinical chemistry (see Section 5.2.1 and Table 8);
- Obtain pre-dose blood sample for disease specific marker (CA-125) (see Section 5.2.1.4 and Table 8);
- Obtain pre-dose blood sample for PGx (see Section 5.6 and Table 8);
- CCI [redacted]
- CCI [redacted]
  CCI [redacted]
- Dispense olaparib;
- Assess and record concomitant medications including history of blood transfusions (within the previous 120 days from informed consent and the reasons); and
- Assess subject for adverse events (continuous from time of informed consent).

4.2.2 Study Visit 3, Day 8 to Visit 5, Day 22

The following procedures will be performed at Visit 3, Day 8; Visit 4, Day 15; and Visit 5, Day 22 (± 3 days):

- Obtain blood sample for hematology/clinical chemistry (see Section 5.2.1 and Table 8);
- Assess and record concomitant medications including blood transfusions; and
- Assess subject for adverse events (continuous from time of informed consent).

4.2.3 Study Visit 6, Day 29

The following procedures will be performed at Visit 6, Day 29 (± 3 days):

- Obtain blood sample for hematology/clinical chemistry (see Section 5.2.1 and Table 8);
- Obtain blood sample for disease specific marker (CA-125) (see Section 5.2.1.4 and Table 8);
- Assess and record concomitant medications including blood transfusions;
- Assess subject for adverse events (continuous from time of informed consent); and
- Dispense/return olaparib.

4.2.4 Study Visit 7, Day 57, and every 4 weeks onwards

Subsequent on-treatment visits for the active treatment period will take place on Day 1 of a 4-week visit period up to 52 weeks (if not progressed and still on treatment), then on Day 1 of a 12-week visit period relative to date of enrollment until PD (RECIST v1.1). Subsequent on-treatment visits for subjects who remain on treatment post-progression should take place every 12 weeks. Tumor assessment visits will be performed at the end of every 8 weeks (± 1 week) up to 48 weeks, then every 12 weeks (± 1 week) relative to date of enrollment until PD (RECIST v1.1). Subjects will be contacted to assess for survival every 12 weeks following disease progression until death, withdrawal of consent, or study closure. See Section 4.4.

The following procedures will be performed at Visit 7, Day 57 (± 3 days) and every 4 weeks onward (i.e., Visit 8 [Day 85], Visit 9 [Day 113], etc.) through the active treatment period:

- Assess functional status using the ECOG performance status scale (see Appendix F);
- Obtain blood sample for hematology/clinical chemistry (see Section 5.2.1 and Table 8);
- Obtain blood sample for disease specific marker (CA-125) (see Section 5.2.1.4 and Table 8);
- Assess tumor (CT or MRI according to RECIST v1.1) (see Section 5.1.1);
  - Note: The tumor assessments according to RECIST v1.1 will be performed every 8 weeks (± 1 week) from the first dose of study drug (Visit 2) for 48 weeks, and then every 12 weeks (± 1 week) (relative to the date of enrollment) thereafter until determined by the Investigator according to RECIST v1.1 criteria (including confirmatory RECIST scan).
- Assess and record concomitant medications including blood transfusions;
- Assess subject for adverse events (continuous from time of informed consent); and
- Dispense/return olaparib.

4.2.5 Study Treatment Discontinuation Visit

Subjects should be discontinued from study treatment if they have objective radiological disease progression according to RECIST v1.1 (see Appendix G) and complete the Study Treatment Discontinuation Visit as per the study plan.

The following procedures will be performed at the Study Treatment Discontinuation Visit (+ 7 days):

- Perform physical examination (see Section 5.2.2);
- Assess functional status using the ECOG performance status scale (see Appendix F);
- Obtain blood sample for hematology/clinical chemistry (see Section 5.2.1 and Table 8);
- Obtain blood sample for disease specific marker (CA-125) (see Section 5.2.1.4 and Table 8);

- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- Assess and record concomitant medications including blood transfusions;
- Assess subject for adverse events (continuous from time of informed consent); and
- Return olaparib.

4.3 Follow-up period

4.3.1 Follow-up 30 days after the last dose of olaparib (Follow-up Visit)

A Follow-up Visit should be conducted 30 days (± 7 days) after the last dose of olaparib. Any SAEs or adverse events ongoing at the time of the Study Treatment Discontinuation Visit or which have occurred during the defined 30-day follow-up period must be followed-up (in accordance with Section 6.3.1). Appropriate safety evaluations should be repeated and/or additional tests performed at any time when clinically indicated, or at the discretion of the Investigator, until resolution, unless, in the Investigator's opinion, the condition is unlikely to resolve due to the subject's underlying disease. If the subject is lost to follow-up, then this should be noted in the eCRF.

The following assessments will be performed:

- Obtain vital signs, body weight, and ECG (see Sections 5.2.3 and 5.2.4);
- Obtain sample for pregnancy test, if necessary (see Section 5.2.5.1);
- Obtain blood sample for hematology/clinical chemistry (see Section 5.2.1 and Table 8);
- Assess and record concomitant medications including blood transfusions;
- Assess subject for adverse events (continuous from time of informed consent) (see Section 6.3.1); and
- Record subsequent cancer therapy following discontinuation of study treatment.

During the follow-up period, subjects will be followed for PFS (CA-125 and radiographic evidence of progression per site standards) until database lock/end of study and assessed for OS.

4.3.2 Follow-up after final data cut-off for the primary endpoint analysis/end of study

After data cut-off for the primary endpoint (ORR), during the additional 12 months of follow-up, subjects will be assessed for adverse events (see Section 6.3.1.1), and assessed for survival every 3 months until the closure of the study.

At the end of the additional 12 months of survival and safety follow-up, the study will be closed. Subjects who are receiving treatment at this time can either choose to discontinue from olaparib, or where the Investigator believes subjects are gaining clinical benefit, subjects may continue to receive olaparib off study. AstraZeneca will continue to supply olaparib after completion of this study until either olaparib tablets are licensed in the US, or it is determined that the benefit-to-risk profile does not support continued development of olaparib, or the FDA has deemed the drug not approvable. In all these scenarios, AstraZeneca will work with Investigators on the proper transition of subjects to alternative therapies if possible.

4.4 Survival follow-up

All subjects who enrolled and received at least 1 dose of olaparib will be followed for survival. Subjects will be contacted to assess for survival status every 12 weeks following disease progression until death, withdrawal of consent, or study closure. Survival information may be obtained via telephone or email contact with the subject, subject's family, or by contact with the subject's current physician. The vital status of the subject can be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws.

5. STUDY ASSESSMENTS

An EDC system will be used for data collection and query handling. The Investigator will ensure that data are recorded in the eCRF as specified in the Clinical Study Protocol and in accordance with the instructions provided.

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

5.1 Efficacy assessments

5.1.1 CT and MRI scans tumor assessments (RECIST v1.1)

The baseline tumor assessment will be performed no more than 28 days prior to study treatment start (Visit 2) and as close as possible to study treatment start. Following the

baseline tumor assessment, subsequent tumor assessments according to RECIST v1.1 should be performed at the end of every 8 weeks (± 1 week) from first dose of study drug (Visit 2) for 48 weeks and every 12 weeks (± 1 week) (relative to the date of enrollment) thereafter until PD. If an unscheduled assessment was performed and the subject has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits. Subjects who are determined to have PD according to RECIST v1.1 criteria (including confirmatory RECIST scan) by the Investigator may have additional scans performed per the site's standard of care. All treatment decisions will be based on the Investigator's assessment of the scans.

A copy of all tumor assessment scans will be collected by an AstraZeneca Representative through disease progression.

All subjects should have RECIST assessments until documented evidence of objective radiological progression in accordance with RECIST v1.1, irrespective of treatment decisions (i.e., RECIST follow-up until progression even if a subject discontinues study treatment prior to progression and/or receives a subsequent therapy prior to progression).

At baseline, the imaging modalities used for RECIST assessment will be CT (MRI where CT is contraindicated) scans of the chest, abdomen, and pelvis, with other regions as clinically indicated for the assessment of disease. Follow-up CT or MRI assessments (per RECIST v1.1) will be by chest (in those subjects 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. The methods of assessment of tumor burden used at baseline must be used at each subsequent follow-up assessment. A CT examination with intravenous contrast media administration is the preferred method. An MRI should be used where CT is not feasible or it is medically contraindicated. For brain lesion assessment, MRI is the preferred method. Subjects must be followed-up until RECIST disease progression.

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

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

5.1.2 Tumor evaluation

RECIST v1.1 criteria will be used to assess subject response to treatment for determination of PFS times, ORR, and DoR. The RECIST v1.1 guidelines for measurable, non-measurable, target and non-target lesions (TLs), and the objective tumor response criteria (CR, PR, SD, or PD) are presented in Appendix G.

Note: The biopsied tumor sample taken at screening should not be assessed as a TL as part of the RECIST assessments if there are other lesions available. The biopsy should be taken after the baseline scan has been performed.

Although CA-125 is measured in this study, it will not be directly used for assessing objective response or progression, and subjects should be continued on treatment until objective radiological disease progression as per RECIST v1.1 as assessed by the Investigator, or when they meet any discontinuation criteria (see Section 3.9). After documentation of disease progression, subjects will be followed for survival.

If the Investigator is in doubt as to whether progression has occurred, particularly with response to non-TL or the appearance of a new lesion, treatment should continue until the next scheduled assessment, or sooner if clinically indicated, and the Investigator should reassess the subject'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 the 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 1 or more non-TLs is usually not sufficient to qualify for unequivocal progression status.

5.2 Safety assessments

For the timing of individual measurements, refer to the study plan (see Table 6). Adverse events will be collected continuously throughout the active treatment period including the follow-up period.

5.2.1 Laboratory safety assessments

Blood and urine samples for determination of clinical chemistry, hematology, coagulation, and urinalysis will be taken at the times indicated in the study plan (see Table 6). Note: Safety blood samples (e.g., clinical chemistry, hematology, coagulation, etc.) do not need to be repeated on Visit 2 (Day 1) of the study treatment if assessed at least 3 weeks after the last dose of chemotherapy but within 7 days before starting study treatment, unless the Investigator believes the values are likely to have changed significantly.

Additional safety samples (e.g., clinical chemistry, hematology, coagulation, etc.) 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 investigative site. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site.

The following laboratory variables will be measured:

Table 7 Laboratory Safety Variables

Hematology/Hemostasis (whole blood)	Clinical Chemistry (serum or plasma)
B-Hemoglobin	S/P-Creatinine
B-Leukocyte count	S/P-Bilirubin, total
B- Leukocyte differential count (absolute count)	S/P-Alkaline phosphatase
B-Platelet count	S/P-Aspartate transaminase
B-Absolute neutrophil count	S/P-Alanine transaminase
	S/P-Albumin
Urinalysis (dipstick)	S/P-Potassium
U-Hb/erythrocytes/blood	S/P-Calcium, total
U-Protein/albumin	S/P-Sodium
U-Glucose	S/P-Urea or blood urea nitrogen

B = blood; P = plasma; S = serum; U = urine.

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

In case a subject shows an AST **or** ALT ≥ 3 × ULN **or** TBL ≥ 2 × ULN, please refer to Appendix D, for further instructions.

5.2.1.1 Coagulation

Activated partial thromboplastin time (APTT) will be performed if clinically indicated.

International normalized ratio (INR) will be performed if clinically indicated unless the subject is receiving warfarin. Subjects taking warfarin may participate in this study; however, it is recommended that INR be monitored carefully at least once per week for the first month, then monthly if the INR is stable.

Each coagulation test result will be recorded in the eCRF.

5.2.1.2 Urinalysis

Urinalysis by dipstick should be performed as stated in Table 6. Microscopic analysis should be performed by the hospital's local laboratory, if required, checking for the safety variables listed in Table 7. For information on how adverse events based on laboratory tests should be recorded and reported, see Section 6.3.

5.2.1.3 Bone marrow or blood cytogenetic samples

Bone marrow or blood cytogenetic samples may be collected for subjects with prolonged hematological toxicities as defined in Section 6.7.1.

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

5.2.1.4 Disease specific tumor marker samples (CA-125)

As part of the routine safety blood samples, all subjects will supply blood samples for CA-125 (2 mL) assessment at the beginning of each 4-week period prior to the subject receiving study treatment.

It is important to follow the assessment schedule as closely as possible. If CA-125 assessment is performed outside of the scheduled visit ± 1-week window interval, every attempt should be made to assess the CA-125 at the scheduled time points. Subjects will be evaluated until objective disease progression (RECIST v1.1), based on progressive serial elevation of serum CA-125 according to the modified GCIG criteria. For the modified GCIG criteria, see Appendix H.

Further assessment of CA-125 post-serological progression will be at the discretion of the Investigator according to local clinical practice.

Objective response rates based on the Investigator review of RECIST v1.1, CA-125 response rates, and the percentage of subjects who had a RECIST response and/or a CA-125 response will be summarized.

5.2.2 Physical examination

A complete physical examination will be performed and will include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose, and throat), lymph nodes, thyroid, musculo-skeletal (including spine and extremities), and neurological systems. Note: After the baseline assessment it is not necessary to record the details on an eCRF unless the details are related to an adverse event/SAE.

5.2.3 ECG

5.2.3.1 Resting 12-lead ECG

The ECG at screening should be performed within 7 days prior to starting the study treatment. Electrocardiograms will also be performed at Day 1 and at the Follow-up Visit. Electrocardiograms will be performed according to local practice with the site's ECG equipment.

Twelve-lead ECGs will be obtained after the subject has been rested in a supine position for at least 5 minutes in each case. The Investigator or qualified 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.

Electrocardiograms will be recorded at 25 mm/sec. All ECGs should be assessed by the Investigator as to whether they are clinically significantly abnormal/not clinically significantly abnormal. If there is a clinically significant abnormal finding, the Investigator will record it as an adverse event in the eCRF. The original ECG traces must be stored in the subject medical record as source data.

5.2.4 Vital signs

Height will be assessed at screening only. Weight will be assessed at screening and as clinically indicated, according to the study plan (see Table 6).

Any changes in vital signs should be recorded as an adverse event, if applicable. For information on how adverse events based on changes in vital signs should be recorded and reported, see Section 6.3.

5.2.4.1 Pulse and blood pressure

Blood pressure and pulse will be assessed at screening, baseline, and at the Follow-up Visit, according to the study plan (see Table 6).

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

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. The measurements and dates at screening, baseline, and at the Follow-up Visit (see Table 6) 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 for women of childbearing potential within 28 days prior to the start of study treatment, on Day 1 of the study prior to commencing treatment, at the time points shown in Table 6 during study treatment and at the 30 day follow up visit. Pregnancy testing for women of childbearing potential should be conducted at regular intervals (e.g., monthly). Tests will be performed by the hospital's local laboratory. If results are positive, the subject is ineligible/must be discontinued from study treatment immediately.

5.3 Other assessments (Not applicable)

5.4 Pharmacokinetics (Not applicable)

5.5 Pharmacodynamics (Not applicable)

5.6 Pharmacogenetics and biomarkers

5.6.1 Overview

Subjects must provide a tumor sample to be considered for the study – the sample can either be an archival sample or a new baseline tumor sample. The sample may be obtained during pre-screening (in advance of the 28-day window) upon obtaining proper consent.

The Myriad testing may be submitted in advance of the 28-day screening window if the subject consents to the appropriate pre-screening informed consent form.

For screening and cohort assignment purposes, all subjects must provide both a blood and a tumor tissue sample for Myriad central laboratory testing. All subjects must provide approximately 10 mL of blood for the prospective Myriad BRCAnalysis CDx® test for subjects with unknown BRCA status or for confirmation of BRCA status for those with previous results. Additionally, all subjects must provide a tumor tissue sample, minimally as 20 tumor slides, for myChoice® HRD screening and analysis of HRRm gene panel status.

CCI [redacted].

CCI [redacted].

CCI [redacted]

Samples for screening and cohort assignment will be shipped directly to the Myriad central laboratory. All other blood and tumor tissue samples collected at baseline and progression will be shipped to Medpace for storage. Samples will be collected, labeled, stored, and shipped as detailed in the laboratory manual.

Prior to any cohorts being closed to enrollment, subjects may enroll in the study and initiate treatment prior to the Myriad BRACAnalysis CDx® and myChoice® HRD tests being reported; however, subjects will not be allocated into a cohort until the results are received by

the Investigator. Once the test results are received by the Investigator, the subject will be allocated into the appropriate cohort. Once a cohort reaches 90 subjects, the cohort will be closed, and subjects may not initiate treatment until their Myriad BRACAnalysis CDx® and myChoice® HRD tests are completed, the results are received by the Investigator, and it is confirmed there is an open cohort available for which the subject is eligible.

All local procedures for genetic counseling must be followed for subjects who do not know their gBRCA status at study entry.

Samples will be collected and shipped after the subject has signed informed consent. Myriad screening test results will be reported back to the investigative site for clinical assessment. Residual blood (or its derivatives) may be used to evaluate future companion diagnostic tests and for additional exploratory work. Note: The Myriad testing may be submitted in advance of the 28-day screening window if the subject consents to the appropriate pre-screening informed consent form.

As part of the subject's consent, residual tumor or blood (or derivatives) may be used to evaluate future 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 (including BRCAm or HRD status and its role in response). Information regarding tumor/blood sample collection can be found in the laboratory manual.

5.6.2 Collection of pharmacogenetic samples

The subject's consent to participate in the PGx research components of the study is mandatory.

The blood sample for genetic research will be obtained from the subjects at Visit 2. Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding subjects who may withdraw due to an adverse event, as such subjects would be important to include in any genetic analysis. If for any reason the sample is not drawn at Visit 2, it may be taken at any visit until the last study visit. Only 1 sample should be collected per subject for PGx during the study.

Samples will be collected, labeled, stored, and shipped as detailed in the laboratory manual.

5.6.3 Storage, re-use, and destruction of pharmacogenetic samples

The processes adopted for the coding and storage of samples for analysis are important to maintain subject confidentiality. Samples MAY be stored for a maximum of 15 years from the end of the study, after which they will be destroyed. DNA is a finite resource that may be used up during analyses. The results of any further analyses will be reported either in the CSR itself or as an addendum, or separately in a scientific report or publication.

For all samples, irrespective of the type of coding used, the DNA will be extracted from the blood sample. The DNA sample will be assigned a unique number, replacing the information

on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated contract laboratory. No personal details identifying the individual will be available to any person (AstraZeneca Representative employee or contract laboratory staff working with the DNA).

The samples and data for genetic analysis in this study will be single-coded. The link between the subject enrollment code and the DNA number will be maintained and stored in a secure environment. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and trace samples for destruction in the case of withdrawal of consent when the subject has requested disposal/destruction of collected samples not yet analyzed.

CCI [redacted]

CCI [redacted]

5.6.7 Labeling and shipment of biological samples

The Principal Investigator ensures that samples are labeled and shipped in accordance with the laboratory manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria); see Appendix B 'International Air Transport Association (IATA) 6.2 Guidance Document.'

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

5.6.8 Chain of custody of biological samples

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

The Principal Investigator at each site will keep full traceability of collected biological samples from the subjects while in storage at the investigative site until shipment or disposal (where appropriate), and will keep documentation of receipt of arrival.

The sample receiver will keep 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.

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

Samples retained for further use will be stored in the AstraZeneca Biobank. For information regarding the logistics for samples see the laboratory manual.

5.6.9 Withdrawal of informed consent for donated biological samples

If a subject 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.

Collection of the biological samples is an integral part of the study; if the subject withdraws consent prior to receiving the first dose, the subject will be withdrawn from further study participation; however, if the subject withdraws consent after receiving the first dose, the subject may continue in the study.

The Principal Investigator will:

- Ensure that the AstraZeneca Representative is immediately notified of the subject's withdrawal of informed consent to the use of donated samples;
- Ensure that biological samples from that subject, if stored at the investigative site, are immediately identified, disposed of /destroyed, and the action documented;

- Ensure 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; and

- Ensure that the subject and the AstraZeneca Representative are informed about the sample disposal.

The AstraZeneca Representative will ensure that the central laboratory(ies) holding the samples is/are immediately informed about the withdrawn consent to use donated biological samples, and that samples are disposed of/destroyed and the action documented and returned to the study site.

5.7 Blood volume

The total study volume of blood that will be drawn from each subject will vary, depending upon the length of time that the subject remains in the study and on treatment.

Safety laboratory assessments will be performed locally at each study site's laboratory by means of their established methods. The number of samples/blood volumes is therefore subject to site-specific change. For specific information regarding collection and documentation of laboratory samples see the laboratory manual.

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 subject in this study is shown in Table 8.

Table 8 Estimated Maximum Volume of Blood to be Drawn from Each Subject*

Assessment		Sample vol. (mL)	No. of samples - screening	No. of samples Month 1 (Including Day 29)	Months 2-6	Treatment Discontinuation Visit and 30 day Follow-up Visit	Objective radiological disease progression	Total vol. (mL)
Safety	Clinical chemistry (locally assessed)	5	1	5	1(×4)	1(×2)		60
	Hematology (locally assessed)	5	1	5	1(×4)	1(×2)		60
Blood sample: Prospective Myriad *BRCA* test for subjects with unknown *BRCA* status or for confirmation of *BRCA* status for those with previous results		10	1					10
CCI								
CCI								
Blood cytogenetic analysis		Site dependent	Depends on the blood smear result					
Serum pregnancy test		Site dependent	Site may use urine instead	Site may use urine instead				
Blood sample for CA-125 (locally assessed)		2	1	1(×2)	1(×4)	1(×1) (only treatment discontinuation visit)		16
CCI								
Total volume (mL)			CCI					

*The total study volume of blood that will be drawn from each subject will vary, depending upon the length of time that the subject remains in the study and on treatment.
CA = Cancer antigen; CCI ; No. = number; vol. = volume.

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

The Principal Investigator 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 (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, ECG). In clinical studies, an adverse event can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term adverse event is used to include both serious and non-serious adverse events.

6.1.1 Olaparib adverse events of special interest

Adverse events of special interest (AESI) are events of scientific and medical interest specific to the further understanding of olaparib's safety profile and that require close monitoring and rapid communication by the Investigators to the AstraZeneca Safety Representative. An AESI may be serious or non-serious. However, AESIs for olaparib should be considered as SAEs as they are medically important and have been identified as important potential risks for olaparib that are under close surveillance at AstraZeneca. The olaparib AESIs include MDS/AML, new primary malignancy (other than MDS/AML), and pneumonitis.

ANY event of suspected or confirmed MDS/AML, new primary malignancy, or pneumonitis, regardless of the severity, should be treated as an SAE and reported to the AstraZeneca Safety Representative according to SAE reporting processes and timelines (see Section 6.4).

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

6.2 Definitions of serious adverse event

An SAE is an adverse event occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that fulfills 1 or more of the following criteria:

- Results in death;
- Is immediately life-threatening;
- Requires in-subject 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; or
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent 1 of the outcomes listed above.

For further guidance on the definition of an SAE, see Appendix A to the Clinical Study Protocol. For additional information on SAE reporting, see Section 6.4.

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

Adverse events will be collected from time of signature of first informed consent for participating in the study, continuously throughout the active treatment period including the follow-up period.

Serious adverse events will be recorded from the time of informed consent for participating in the study. See Section 6.4.

After the data cut-off for the primary and secondary endpoint analyses, any ongoing adverse events/SAEs will be followed for resolution and included in the AstraZeneca Safety Database.

6.3.1.1 Adverse events after the 30 day follow-up period

For pharmacovigilance purposes and characterization, any case of MDS/AML or new primary malignancy occurring after the 30 day follow-up period should be reported to the AstraZeneca Safety Representative whether it is considered a non-serious adverse event (e.g., non-melanoma skin cancer) or an SAE, and regardless of the Investigator's assessment of causality. Investigators will be asked during the regular follow-up for survival if the subject has developed MDS/AML or a new primary malignancy, and will be prompted to report any such cases.

At any time after a subject has completed the study (i.e., no longer receiving study drug and past the 30 day follow-up period), if an Investigator learns of any SAE, including sudden death of unknown cause, and he/she considers there is a reasonable possibility that the event is causally related to olaparib, the Investigator should notify the AstraZeneca Safety Representative.

Otherwise, after study treatment completion (i.e., after any scheduled post-treatment follow-up period has ended), there is no obligation to actively report information on new adverse events or SAEs occurring in former study subjects.

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, until the condition stabilizes, is judged by the Investigator to be no longer clinically significant, or until the subject is lost to follow-up. AstraZeneca retains the right to request additional information for any subject with ongoing adverse event(s)/SAE(s) at the end of the study, if judged necessary.

6.3.3 Variables

The following variables will be collected for each adverse event:

- Adverse event (verbatim),
- The date when the adverse event started and stopped,
- CTCAE grade and changes in CTCAE grade,
- Whether the adverse event is serious or not,
- Investigator causality rating against olaparib (yes or no),
- Action taken with regard to olaparib,
- Outcome, and
- Adverse event caused subject's withdrawal from study (yes or no).

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

- Date adverse event met criteria for an SAE,
- Date Investigator became aware of an SAE,
- Adverse event is serious due to,
- Date of hospitalization,
- Date of discharge,
- Probable cause of death,
- Date of death,
- Autopsy performed,
- Causality assessment in relation to study procedure(s),

- Causality assessment in relation to other medication, and
- Description of adverse event.

Severity of adverse event

For each episode of an adverse event, all changes to the CTCAE grade attained, as well as the highest attained CTCAE (version 4.03) grade, should be reported.

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

The grading scales found in the National Cancer Institute (NCI) CTCAE version 4.03 will be 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 the CTCAE version 4.03 can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

6.3.4 Causality collection

The Investigator will assess causal relationship between olaparib and each adverse event, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

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

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

6.3.5 Adverse events based on signs and symptoms

All adverse events spontaneously reported by the subject or 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 adverse events, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

6.3.6 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 to baseline in protocol-mandated laboratory values, vital signs, and ECG abnormalities should therefore only be reported as adverse events if 1 of the following is met:

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

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an adverse event, and the associated laboratory result/vital sign will be considered as additional information. Wherever possible, the reporting Investigator should use the clinical, rather than the laboratory term (e.g., anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as adverse event(s).

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

6.3.7 Hy's Law

Potential Hy's Law cases where a subject shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN and may need to be reported as SAEs. Confirmed Hy's Law cases should always be reported as SAEs. Please refer to Appendix D for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

6.3.8 Disease progression

Disease progression can be considered as a worsening of a subject's condition attributable to the disease for which olaparib is 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 adverse event. Events which are unequivocally due to disease progression should not be reported as adverse events during the study.

For this study, objective radiological disease progression will be determined as per RECIST v1.1. See Appendix G.

6.3.9 New cancers

The development of a new primary cancer (including skin cancer) should be regarded as an adverse event (see Section 6.1.1 Olaparib Adverse Events of Special Interest). New primary malignancies are those that are not the primary reason for the administration of the study treatment and have developed after the inclusion of the subject 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 adverse event/SAE, as they are considered to be disease progression.

6.3.10 Lack of efficacy

When there is deterioration in the cancer for which the study treatment(s) is being used, there may be uncertainty as to whether this is lack of efficacy or an adverse event. In such cases, unless the Sponsor or the reporting physician considers that the study treatment contributed to the deterioration of the condition, the deterioration should be considered to be a lack of efficacy and not an adverse event.

6.3.11 Deaths

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

- Death that is clearly the result of disease progression should be reported to the study monitor at the next monitoring visit and should be documented in the death eCRF, but should not be reported as an SAE.
- Where death is not due (or not clearly due) to progression of the disease under study, the adverse event causing the death must be reported to the AstraZeneca Safety Representative as an SAE within 24 hours (see Section 6.4 for further details). The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death. This information can be captured in the death eCRF.
- Deaths with an unknown cause should always be reported as SAEs. A post-mortem evaluation may be helpful in the assessment of the cause of death, and if performed, a copy of the post-mortem results should be forwarded to the AstraZeneca Safety Representative within the usual timeframes.

6.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to olaparib or to the study procedure(s). All SAEs will be recorded in the eCRF. See Section 6.3 for adverse event recording information.

If any SAE occurs in the course of the study, then Investigators or other site personnel will inform the appropriate AstraZeneca Safety Representatives **within 1 day**, i.e., immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca Safety Representatives will work with the Investigator to ensure that all the necessary information is provided to the AstraZeneca 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 will inform AstraZeneca Safety Representatives of any follow-up information on a previously reported SAE **within 1 calendar day**, i.e., 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 adverse event is serious in the EDC system, an automated email alert is sent to the designated AstraZeneca Safety Representative.

If the EDC system is not available, then the Investigator or other study site personnel will report an SAE to the appropriate AstraZeneca Safety Representative by telephone. If the eCRF is not available, paper back-up forms should be used (including SAE, pregnancy, and overdose forms).

The AstraZeneca Safety Representative will advise the Investigator/study site personnel how to proceed.

Safety Contact Information: Medpace Clinical Safety

Medpace SAE hotline – USA:
Telephone: +1-800-730-5779, ext. 12999 or +1-513-579-9911, ext. 12999
Fax: +1-866-336-5320 or +1-513-579-0444
e-mail: medpace-safetynotification@medpace.com

6.5 Overdose

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

Olaparib must only be used in accordance with the dosing recommendations in this protocol. Any dose or frequency of dosing that exceeds the dosing regimen specified in this protocol should be reported as an overdose. The maximum tolerated dose is 300 mg *bid* (tablet).

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

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

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

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

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

6.6 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to the AstraZeneca Safety Representative.

6.6.1 Maternal exposure

If a subject becomes pregnant during the course of the study, olaparib should be discontinued immediately.

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

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the olaparib 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 adverse events. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed-up and documented even if the subject was discontinued from the study.

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

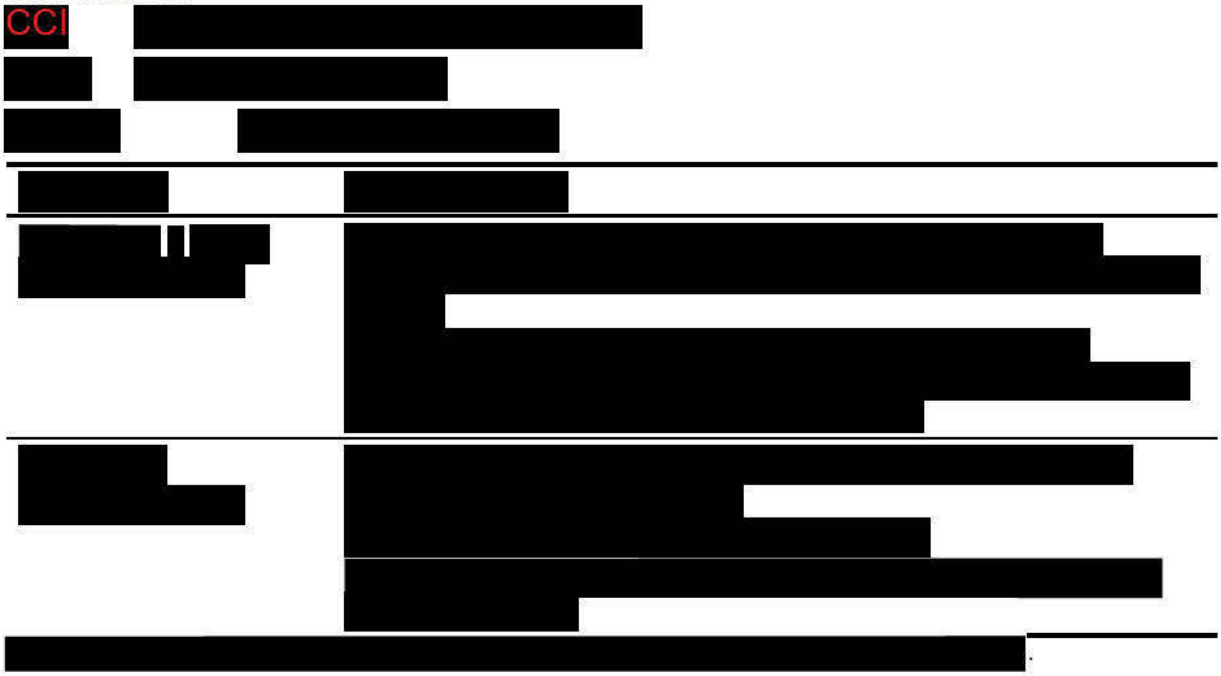
The designated AstraZeneca Safety Representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca data entry site **within 1 or 5 calendar days** for SAEs (see Section 6.4) and **within 30 days** for all other pregnancies.

The same timelines apply when outcome information is available.

6.6.2 Paternal exposure (Not applicable)

CCI [redacted]

CCI [redacted]



If a subject experiences a dose interruption > 4 weeks, the subject cannot restart study medication. See Section 6.7.

Common treatable causes of anemia (e.g., iron, vitamin B12, or folate deficiencies and hypothyroidism) should be investigated and appropriately managed. In some cases, management of anemia may require blood transfusions. For cases where subjects develop prolonged hematological toxicity (≥ 2 week interruption/delay in study treatment due to CTCAE grade 3 or worse anemia and/or development of blood transfusion dependence), refer to Section 6.7.1.3.

CCI [redacted]

CCI [redacted]

If a subject experiences a dose interruption > 4 weeks the subject cannot restart study medication. See Section 6.7.

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

Primary prophylaxis with Granulocyte colony-stimulating factor (G-CSF) is not recommended; however, if a subject develops febrile neutropenia, study treatment 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 (7 days for PEGylated G-CSF) of the last dose of study treatment unless absolutely necessary.

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

For cases where subjects develop prolonged hematological toxicity (≥ 2 week interruption/delay in study treatment due to CTCAE grade 3 or worse), refer to Section 6.7.1.3.

6.7.1.3 Management of prolonged hematological toxicities while on study treatment

If a subject develops prolonged hematological toxicity such as:

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

Check weekly differential blood counts including reticulocytes and peripheral blood smear. If any blood parameters remain clinically abnormal after 4 weeks of dose interruption, the subject should discontinue olaparib treatment and 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. Study treatment should be discontinued if blood counts do not recover to CTCAE grade 1 or better within 4 weeks of dose interruption.

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

If a subject experiences a dose interruption > 4 weeks the subject cannot restart study medication. See Section 6.7.

6.7.2 Management of non-hematological toxicity

Repeat dose interruptions are allowed as required, for a maximum of up to 4 weeks on each occasion. If the interruption is longer than 4 weeks, the AstraZeneca Representative Study Physician must be informed. See Section 6.7. When the toxicity reoccurs following re-challenge with study treatment, and where further dose interruptions are considered inadequate for management of toxicity, then the subject should be considered for dose reduction or must permanently discontinue study treatment.

CCI [redacted] Treatment must be interrupted if any NCI-CTCAE grade 3 or 4 adverse event occurs, which the Investigator considers to be related to administration of study treatment.

6.7.2.1 Management of new or worsening pulmonary symptoms

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

Following investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, then study treatment can be restarted, if deemed appropriate by the Investigator. If significant pulmonary abnormalities are identified, these need to be discussed with the AstraZeneca Representative Study Physician.

If a subject experiences a dose interruption > 4 weeks the subject cannot restart study medication. See Section 6.7.

6.7.2.2 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 subjects and 36% of the placebo treated subjects, and vomiting was reported in 34% of the olaparib treated subjects and 14% of the placebo treated subjects. These events are generally mild to moderate (CTCAE grade 1 or 2) in 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 around 9 months and for vomiting around 6 to 7 months.

No routine prophylactic anti-emetic treatment is required at the start of study treatment; however, subjects should receive appropriate anti-emetic treatment at the first onset of nausea or vomiting and as required thereafter, in accordance with local treatment practice guidelines. Alternatively, olaparib tablets can be taken with a light meal/snack (i.e., 2 pieces of toast or a couple of biscuits). Note: For adverse events of nausea and vomiting, an additional eCRF is required.

As per international guidance on anti-emetic use in cancer subjects (European Society for Medical Oncology, National Comprehensive Cancer Network), generally a single agent anti-emetic should be considered, e.g., dopamine receptor antagonist, antihistamines, or dexamethasone.

6.7.2.3 Renal impairment

If subsequent to study entry and while still on study therapy, a subject's estimated creatinine clearance (CrCl) decreases to become < 51 mL/min, retesting should be performed promptly.

A dose reduction is recommended for subjects who meet the following criteria during the course of the study:

- Baseline CrCl ≥ 51 mL/min who have on study a CrCl < 51 mL/min,
- Baseline CrCl < 51 mL/min but had serum creatinine ≤ 1.5 × ULN, and then on study had a clinically meaningful lower CrCl value.

CCI

Olaparib has not been studied in subjects with severe renal impairment (CrCl ≤ 30 mL/min) or end-stage renal disease; if subjects develop severe impairment or end-stage renal disease olaparib must be discontinued.

6.7.2.4 Interruptions for intercurrent non-toxicity related events

Study treatment dose interruption for conditions other than toxicity resolution should be kept as short as possible. If a subject cannot restart study treatment within 4 weeks for resolution of intercurrent conditions not related to disease progression or toxicity, the case should be discussed with the AstraZeneca Representative Study Physician. See Section 6.7.

All dose reductions and interruptions (including any missed doses), and the reasons for the reductions/interruptions, are to be recorded in the eCRF.

Study treatment should be stopped at least 3 days prior to planned surgery. After surgery, study treatment can be restarted when the wound has healed. No stoppage of study treatment is required for any needle biopsy procedure.

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

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

6.8 Study governance and oversight

A Study Steering Committee composed of representatives from AstraZeneca and key Investigators/scientific advisors will be responsible for providing recommendations to US Medical Affairs leadership at AstraZeneca based on Investigator input, review, and oversight of study execution, scientific conduct, and analysis of study data. The accountabilities and

requirements of the Steering Committee members will be outlined in the Steering Committee Charter.

CCI [redacted]

7.2 Dose and treatment regimens

CCI [redacted] Each dosing container will contain sufficient medication for at least 28 days plus overage. CCI [redacted] Sufficient study treatment should be dispensed for at least each treatment period plus overage; however, additional treatment can be dispensed to subjects to last longer in accordance with local practice.

CCI [redacted].

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

If vomiting occurs shortly after the olaparib tablets are swallowed, the dose should only be replaced if all of the intact tablets can be seen and counted. Should any subject enrolled in the study miss a scheduled dose for any reason (e.g., as a result of forgetting to take the tablets or vomiting), the subject 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 subject should take their allotted dose at the next scheduled time.

Subjects will continue with olaparib tablets 300 mg CCI [redacted], from enrollment (Visit 2) until objective radiological disease progression per RECIST v1.1 as assessed by the Investigator, or when they meet any discontinuation criteria (see Section 3.9).

Once subjects have been discontinued from the active treatment period of the study, other treatment options during the survival follow-up period will be at the discretion of the

Investigator. Subjects who continue to gain clinical benefit are allowed to continue olaparib post-study completion. AstraZeneca will continue to supply olaparib tablets after completion of this study until olaparib tablets are approved and commercially available and subjects will then be transferred to commercially available olaparib tablets.

Dose Reductions

For guidance on dose reductions for management of adverse events, refer to Section 6.7.

For guidance on dose reductions when concomitant strong or moderate CYP3A inhibitors cannot be avoided, see Section 7.7.

7.3 Labeling

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

7.4 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. The olaparib label on the bottle specifies the appropriate storage.

7.5 Compliance

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

Subjects should be given clear instructions on how and when to take their study treatment. Subjects will self-administer olaparib. Study site staff will perform 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 subject but will be retained by the investigative site until reconciliation is completed by the study monitor. All subjects must return their bottle(s) of olaparib at the appropriate scheduled visit, when a new bottle will be dispensed. Subjects will be instructed to notify study site personnel of missed doses.

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

7.6 Accountability

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

The study site personnel or study monitor will account for olaparib received at the site, unused study drugs, and for appropriate destructions. Certificates of delivery, destruction, or return should be signed.

Study drug will not be distributed to the study site until the contract is concluded between the study site and the AstraZeneca Representative. The IP Storage Manager is responsible for managing the study medication from receipt by the study site until the return of all unused study medication to the AstraZeneca Representative. AstraZeneca will provide the study documents 'Procedures for drug accountability' and 'Procedures for drug storage,' which describe the specific requirements. The Investigator(s) is responsible for ensuring that the subject has returned all unused study medication.

7.7 Concomitant and other treatments

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

Medications that may NOT be administered

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

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

Restricted concomitant medications

Strong or Moderate CYP3A inhibitors

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

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

- Strong CYP3A inhibitors – reduce the dose of olaparib to 100 mg *bid* for the duration of concomitant therapy with the strong inhibitor and for 5 half-lives afterwards.
- Moderate CYP3A inhibitors – reduce the dose of olaparib to 150 mg *bid* for the duration of concomitant therapy with the moderate inhibitor and for 3 half-lives afterwards.

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

Strong or Moderate CYP3A inducers

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

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

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

P-gp inhibitors

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

Effect of olaparib on other drugs

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

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

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

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

Examples of substrates include:

- CYP3A4 – hormonal contraceptive, simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and quetiapine
- CYP2B6 – bupropion, efavirenz
- CYP2C9 – warfarin
- CYP2C19 – lansoprazole, omeprazole, S-mephenytoin
- P-gp – simvastatin, pravastatin, digoxin, dabigatran, colchicine
- OATP1B1 – bosentan, glibenclamide, repaglinide, statins, valsartan

- OCT1, MATE1, MATE2K – metformin
- OCT2 – serum creatinine
- OAT3 – furosemide, methotrexate

Anticoagulant therapy

Oral anticoagulants are permitted. Subjects who are taking warfarin may participate in this study; however, it is recommended that INR be monitored carefully at least once per week for the first month, then monthly thereafter, if the INR is stable. For Coumadin-like agents, prothrombin time should be checked at baseline and followed closely (as clinically indicated). Subcutaneous heparin and low molecular weight heparin are permitted.

Anti-emetics/Anti-diarrheals

From screening onwards, should a subject develop nausea, vomiting, and/or diarrhea, then these symptoms should be reported as adverse events (see Section 6) and appropriate treatment of the event should be given.

Palliative radiotherapy

Palliative radiotherapy may be used for the treatment of pain at the site of bony metastases that were present at baseline, provided the Investigator does not feel that these are indicative of clinical disease progression during the study period. Study treatment should be discontinued for a minimum of 3 days before a subject undergoes therapeutic palliative radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered (i.e., if a subject has not recovered from bone marrow toxicity within 4 weeks they should be discontinued from the study).

Administration of other anti-cancer agents

Subjects must not receive any other concurrent anti-cancer therapy, including investigational agents, while on study treatment. Subjects 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 beginning study treatment.

Subsequent therapies for cancer

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

7.7.1 Other concomitant treatment

Medications other than those described above, which are considered necessary for the subject's safety and wellbeing, may be given at the discretion of the Investigator and recorded in the appropriate sections of the eCRFs.

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

7.8 Post-study access to study treatment

Subjects are permitted to continue to receive olaparib beyond the closure of the study efficacy database if, in the opinion of the Investigator, they are continuing to receive benefit from treatment with olaparib. During this time, AESIs and SAEs must still be collected and reported until 30 days after the subject finally stops taking olaparib.

Subjects will be followed-up for survival assessments every 12 weeks following disease progression. See Section 4.4.

Subsequent anti-cancer treatment is expected to be initiated following cancer recurrence or development of a new cancer. Information on subsequent PARP inhibitors or other cancer therapies (therapies given, not duration or clinical outcomes) should be recorded in the appropriate eCRFs.

8. STATISTICAL ANALYSES

8.1 Statistical considerations

- All statistical analyses will be performed by AstraZeneca or its representatives.

A comprehensive Statistical Analysis Plan (SAP) will be prepared and any subsequent amendments will be documented, with final amendments completed prior to database lock. Data will be summarized for all subjects who have received at least 1 dose of olaparib and will be presented by cohort.

8.2 Sample size estimate

This is a non-comparative Phase II study and each of the 4 cohorts will be analyzed separately; no statistical comparison will be made between the cohorts. CCI

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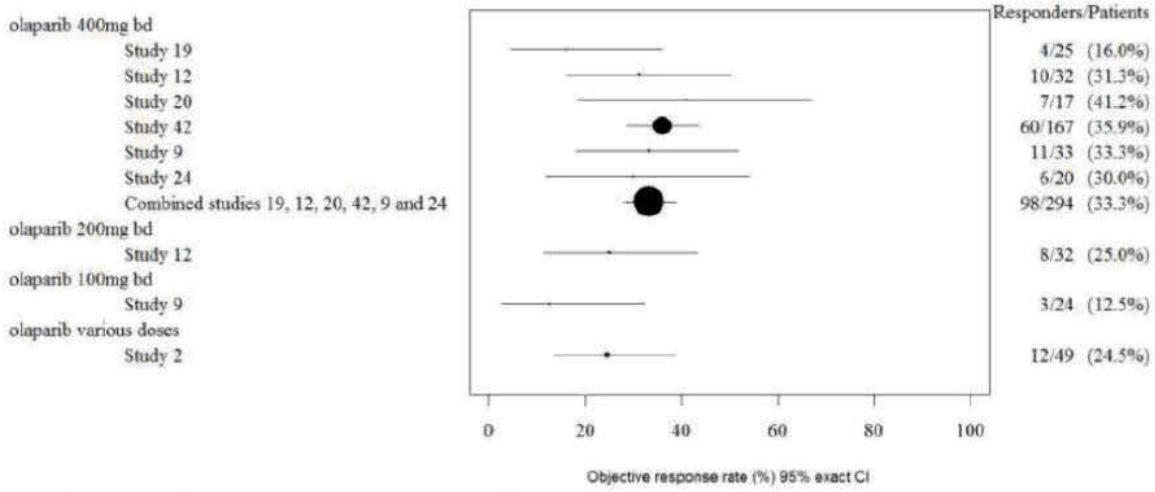
Olaparib, administered as monotherapy to date, has reported ORRs in genetic BRCAm ovarian cancer in excess of 30%. A Forest plot of ORR across all monotherapy studies of olaparib (capsules formulation) is shown in Figure 4.

Figure 4 Forest Plot of ORR Across All Monotherapy Studies of Olaparib in BRCA Mutated Ovarian Cancer



Responders are patients having a best objective response of complete response or partial response.

Note: In all studies shown above except Study D0810C00019 (Study 19), *BRCA* mutation status was based on assessment of *gBRCA* mutation status only.
bd = twice daily; CI = confidence interval; gBRCA = germline BRCA; ORR = objective response rate.

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8.3 Definitions of analysis sets

Table 13 provides a summary of outcome variables and analysis populations.

Table 13 Summary of Outcome Variables and Analysis Populations

Outcome Variable	Population
Efficacy Data	
- Primary: ORR	Efficacy
- Secondary: DoR, CA-125 RR[a], DCR, PFS, TTAP, OS, HRRm	Efficacy
- Demography	Safety
Safety Data	
- Adverse events	Safety
- Laboratory measurements	Safety
- Vital signs	Safety

a. CA-125 RR will be analyzed on a subset of the efficacy analysis set (i.e., excluding subjects whose baseline CA-125 level is not ≥ 2 × ULN and/or not assessed within 2 weeks of starting treatment with olaparib).

CA = Cancer antigen; CA-125; CA-125 RR = CA-125 response rate; DCR = disease control rate; DoR = duration of response; HRRm = homologous recombination repair mutation; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors; TTAP = time to any progression (earliest of CA-125, RECIST, or death); ULN = upper limit or normal.

8.3.1 Efficacy analysis set

The efficacy analysis set comprises all subjects who received at least 1 dose of olaparib and had a baseline tumor assessment.

8.3.2 Safety analysis set

The safety analysis set comprises all subjects who received at least 1 dose of olaparib.

8.4 Outcome measures for analyses

8.4.1 Calculation or derivation of efficacy variable(s)

At each visit, subjects will be assigned a visit response of CR, PR, SD, PD, or not evaluable (NE) based on RECIST v1.1 guidelines, based on the Investigator's assessment.

8.4.2 Primary endpoint

The ORR rate is defined as the percentage of subjects with measurable disease with at least 1 visit response of CR or PR that is confirmed at least 4 weeks later. 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 that occurred after a further anti-cancer therapy was received will not be included in the numerator for the ORR calculation. Subjects lacking valid data to assign a response status will be included in the denominator for the response rate calculation based on the efficacy analysis set.

In the case where a subject has 2 non-consecutive visit responses of PR, then, as long as the time between the 2 visits of PR is greater than 4 weeks and there is no PD between the PR visits, the subject will be defined as a responder. Similarly, if a subject has visit responses of CR, NE, CR, then as long as the time between the 2 visits of CR is greater than 4 weeks, a best response of CR will be assigned.

8.4.3 Secondary endpoints

8.4.3.1 Duration of response

The DoR will be defined as the time from the date of first documented response (that is subsequently confirmed) until the date of documented objective PD or death in the absence of PD. The end of response should coincide with the date of PD or death from any cause used for the PFS endpoint. The time of the initial response will be defined as the latest of the dates contributing towards the first visit response of PR or CR. If the response is not confirmed (per RECIST v1.1), it will not be included. If a subject does not progress following a response, then the subject's DoR will use the PFS censoring time.

8.4.3.2 CA-125 response rate

The CA-125 response will be based upon the latest GCIG guidelines. Serum samples will be collected for CA-125 tumor markers on all subjects at baseline (within 2 weeks prior to Cycle 1, Day 1), Day 1 of each cycle, and at the End-of-Study Treatment Visit.

A response according to CA-125 has occurred if there is at least a 50% reduction in CA-125 levels from the baseline sample. The response must be confirmed and maintained for at least 28 days. Subjects can be evaluated according to CA-125 only if they have a baseline sample that is at least twice the ULN and within 2 weeks prior to starting treatment.

Those subjects who have both a CA-125 response and whose CA-125 level falls to within the normal range, can be classified as CA-125 complete responders.

The CA-125 response rate is defined as the percentage of subjects achieving a CA-125 response. The CA-125 CR Rate is defined as the percentage of subjects achieving a CA-125 response with the CA-125 level additionally falling within the normal range. The CA-125 response rate will be analyzed on a subset of the efficacy analysis set (i.e., excluding subjects whose baseline CA-125 level is not ≥ 2 × ULN and/or not assessed within 2 weeks of starting treatment with olaparib) (Rustin et al 2011).

8.4.3.3 Disease control rate

The DCR is defined as the percentage of subjects who have a best overall response of confirmed CR or PR or SD at ≥ 8 weeks divided by the number of subjects in the efficacy analysis set, prior to any PD event.

8.4.3.4 Progression-free survival

Progression-free survival is defined as the time from the date of first dose of olaparib until the date of objective radiological disease progression (Investigator assessed via RECIST v1.1) or death (by any cause in the absence of disease progression) regardless of whether the subject withdraws from therapy or receives another anticancer therapy prior to disease progression. Subjects 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 efficacy assessment. However, if the subject progresses or dies after 2 or more missed visits, the subject will be censored at the time of the latest evaluable assessment. Given the scheduled visit assessment scheme, 2 missing visits will equate to more than 18 weeks (or 26 weeks after 1 year) since the previous RECIST v1.1 assessment, allowing for early and late visits. If the subject has no evaluable visits or does not have a baseline assessment, they will be censored at Day 1 unless they die within 2 visits of baseline (18 weeks allowing for visit window).

The PFS time will always be derived based on scan/assessment dates and not visit dates. 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 assessment/scan dates of the component that triggered the progression.
- When censoring a subject for PFS, the subject will be censored at the latest of the assessment/scan 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 radiological progression is defined as at least a 20% increase in the sum of the diameters of the TLs (compared to previous minimum sum) and an absolute increase of > 5 mm, an overall non-TL assessment of progression, or a new lesion.

8.4.3.5 Time to earliest progression by RECIST or CA-125, or death

The CA-125 progression will be based upon the latest GCIG guidelines. Progression or recurrence based on serum CA-125 levels will be defined on the basis of a progressive serial elevation of serum CA-125 according to the following criteria:

- Subjects with elevated CA-125 pre-treatment and normalization of CA-125 must show evidence of CA-125 ≥ 2 × ULN on 2 occasions at least 1 week apart;
- Subjects with elevated CA-125 before treatment, which never normalizes, must show evidence of CA-125 ≥ 2 times the nadir value on 2 occasions at least 1 week apart; or
- Subjects with CA-125 in the reference range before treatment must show evidence of CA-125 ≥ 2 × ULN on 2 occasions at least 1 week apart.

Cancer antigen-125 progression will be assigned the date of the first measurement that meets the criteria as noted. Subjects are not evaluable for CA-125 if they have received mouse antibodies (unless the assay used has been shown not to be influenced by human anti-mouse antibody) or if there has been medical and/or surgical interference with their peritoneum or pleura (e.g., paracentesis) during the previous 28 days.

For the purpose of this endpoint, a subject may be declared to have PD on the basis of either the objective RECIST v1.1 criteria or the GCIG CA-125 criteria. The date of progression will be the date of the earlier of the 2 events if both are documented.

Time to earliest progression is defined as the time from the date of the first dose of olaparib until the earliest of CA-125 progression or RECIST progression, or death from any cause. Subjects without a CA-125 progression or objective radiological progression by RECIST v1.1 who are still alive at the time of analysis will be censored at their last evaluable RECIST assessment or their last available CA-125 measurement, whichever is the most recent at the time of analysis. If a subject progresses or dies after 2 or more missed RECIST and CA-125 assessments, then the subject will be censored at the time of their last evaluable assessment.

8.4.3.6 Overall survival

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

Assessments for survival should be made every 12 weeks following disease progression. Survival information may be obtained via telephone contact with the subject, subject's family, or the subject's current physician. Survival data will be collected at the time of database lock for ORR and again at the end of the 12-month follow-up. Survival calls will be performed in the week following the date of data cut-off for the analysis, and if subjects are confirmed to be alive or if the death date is past the data cut-off date, then these subjects will be censored at the date of data cut-off.

8.4.3.7 HRRm status

Subjects in the 2 BRCAwt cohorts (myChoice® HRD positive or negative) will have their HRRm status tested and will be categorized as HRRm positive or HRRm negative. Data from these 2 BRCAwt cohorts will be combined and clinical outcomes will be presented according to HRRm status (HRRm positive versus HRRm negative).

8.4.4 Calculation or derivation of safety variable(s)

Safety and tolerability will be assessed in terms of adverse events (including SAEs and adverse events leading to discontinuation), deaths, laboratory data, and vital signs. These will be collected for all subjects. The number of subjects experiencing each adverse event (based on Medical Dictionary for Regulatory Activities [MedDRA] preferred term) will be summarized by CTCAE grade.

8.4.5 Other significant adverse events

During the evaluation of the adverse event data, an AstraZeneca Representative medically qualified expert will review the list of adverse events that were not reported as an SAE or a discontinuation of olaparib due to an adverse event. Based on the expert's judgment, significant adverse events of particular clinical importance may, after consultation with the Safety Physician, be considered other significant adverse events and reported as such in the CSR. A similar review of laboratory/vital signs/ECG data will be performed for identification of other significant adverse events. Examples of these are marked hematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction, or significant additional treatment.

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8.5 Methods for statistical analyses

Data will be summarized for all subjects who have received at least 1 dose of olaparib. No statistical tests will be performed; the statistical analyses will be purely descriptive. All analyses will be presented by cohort.

Continuous data will be summarized using descriptive statistics (number of observations, mean, standard deviation, median, minimum, and maximum). Frequencies and percentages

will be used for summarizing categorical (discrete) data. Confidence intervals, when presented, will generally be constructed at the 95% level.

8.5.1 Analysis of the primary variable

The ORR will be presented together with the exact 95% CI according to the Clopper-Pearson method.

8.5.2 Analysis of the secondary variable(s)

The DCR and CA-125 response rate will be presented together with the exact 95% CI according to the Clopper-Pearson method.

Kaplan-Meier plots of PFS will be presented for each cohort of subjects. Summaries of the number and percentage of subjects experiencing a PFS event, and the type of event (progression or death) will be provided along with median PFS and 95% CIs.

The analyses of PFS will be based on Investigator assessment according to RECIST v1.1 guidelines, and using all scans regardless of whether they were scheduled or not. The estimated PFS rates at 6 months, 12 months, and 24 months will be summarized (using the Kaplan-Meier curves) if appropriate.

Other time-to-event endpoints (OS, TTAP, DoR) will be described as for PFS.

The safety analyses will consist of assessment of safety and exposure profiles in terms of adverse events/SAEs, laboratory data/vital signs, and ECG that will be collected for all subjects. Appropriate summaries of laboratory data/vital signs and adverse events/SAEs will be produced for all subjects in the safety analysis set per NCI-CTCAE.

Further details will be provided in the SAP.

8.5.3 Subgroup analysis

Subgroup analyses will not be considered within individual cohorts given the limited sample size.

However, for all subjects in the 2 BRCAwt cohorts (myChoice® HRD positive and negative) clinical outcomes will be presented according to HRRm status (HRRm positive versus HRRm negative).

8.5.4 Interim analysis

In each cohort, an informal interim analysis will take place after 15 subjects have had at least 1 radiologic tumor response assessment in the first 6 months of the study. If no responses (CR or PR) are observed in the first 15 subjects in a cohort, in consultation with the Steering Committee, the cohort will be closed to further enrollment. However, if there is at least 1 confirmed objective response in the first 15 subjects, that would justify continuing enrollment up to a maximum of 90 subjects. Enrollment will continue until these interim analyses have been completed and a decision is made by the Study Steering Committee.

Additionally annual updates of relevant study data may be generated for the purpose of reporting at appropriate oncology conferences, as specified in the SAP.

The stopping boundary for the interim futility analysis was determined from the binomial probabilities. With a true ORR of 5%, a cohort would terminate early for futility (no responders observed in the first 15 subjects) with a probability of 0.463, while with true ORRs of 10%, 20%, 40%, and 50%, a cohort would terminate early for futility with probabilities of 0.206, 0.0352, 0.0005, and < 0.0001, respectively.

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9. STUDY AND DATA MANAGEMENT

9.1 Training of study site personnel

Before the first subject 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 EDC system utilized.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator 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 contact 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 medication accountability checks are being performed;

- Perform source data verification (a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (e.g., clinic charts); and

- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject.

The AstraZeneca Representative will be available between visits if the Investigator(s) or other staff at the site needs information and advice about the study conduct.

9.2.1 Source data

Refer to the Clinical Study Agreement for location of source data.

9.2.2 Study agreements

The Principal Investigator at each site should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the terms of the Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of subjects, and in all other respects not relating to study conduct or treatment of subjects, the terms of the Clinical Study Agreement shall prevail.

Agreements between the AstraZeneca Representative and the Principal Investigator should be in place before any study-related procedures can take place, or subjects are enrolled.

9.2.3 Archiving of study documents

The Investigator follows the principles outlined in the Clinical Study Agreement.

9.3 Study timetable and end of the study

All subjects who enrolled and received at least 1 dose of olaparib will be followed for survival. Subjects will be contacted to assess survival every 12 weeks following disease progression until death, withdrawal of consent, or study closure.

A data cut-off for analysis of all primary and secondary endpoints will occur approximately 6 months after the last subject enrolled has commenced study treatment (received at least 1 dose of olaparib). The study will remain open for an additional 12 months after this data cut-off for survival follow-up for applicable subjects. At the end of this additional 12 months of survival follow-up, updated OS and safety analyses will be conducted and the study will be

closed. Subjects are, however, permitted to continue to receive olaparib beyond the closure of the database if, in the opinion of the Investigator, they are continuing to receive benefit from treatment with olaparib. During this time (i.e., the 12 months of survival follow-up), AESIs and SAEs must still be collected and reported until 30 days after the subject finally stops taking olaparib. See Sections 6.3.1, 6.3.1.1, and 6.4 for details of adverse event/SAE reporting.

The anticipated enrollment period is approximately 20 months. The study is expected to start in approximately Q4 2016 and to end by approximately Q1 2020.

The study may be terminated at individual sites if the study procedures are not being performed according to Good Clinical Practice (GCP), or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with olaparib. See Section 3.11.

9.4 Data management by Medpace

Data management will be performed by Medpace, according to the Data Management Plan.

Adverse events and medical/surgical history will be classified according to the terminology of the latest version of MedDRA. Medications will be classified according to the AstraZeneca Drug Dictionary. Classification coding will be performed by Medpace.

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

Data queries will be raised for inconsistent, impossible, or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The Data Management Plan will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process.

When all data have been coded, validated, signed, and locked, clean file will be declared and the final database will be locked.

SAE reconciliation

Serious adverse event reconciliation reports are produced and reconciled with the Patient Safety Database and/or the investigational site.

Data associated with human biological samples

Data associated with biological samples will be transferred from the laboratory(ies) (internal or external) to the AstraZeneca Representative.

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 Subject 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 subjects, 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 subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, an AstraZeneca Representative Study Physician or an Investigator might know a subject's identity and also have access to her genetic data. Also, Regulatory Authorities may require access to the relevant files, though the subject's medical information and the genetic files would remain physically separate.

10.3 Ethics and regulatory review

An institutional review board (IRB) should approve the final Clinical Study Protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the subjects. The Investigator will ensure the distribution of these documents to the applicable IRB, and to the study site staff.

The opinion of the IRB should be given in writing. The Investigator should submit the written approval to an AstraZeneca Representative before enrollment of any subject into the study.

The IRB should approve all advertising used to recruit subjects for the study.

An AstraZeneca Representative 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 IRB annually.

Before enrollment of any subject into the study, the final Clinical Study Protocol, including the final version of the Informed Consent Form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

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

AstraZeneca will provide Regulatory Authorities, IRBs, and Principal Investigators with safety updates/reports according to local requirements.

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

10.4 Informed consent

The Principal Investigator(s) at each site will:

- Ensure each subject is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study;
- Ensure each subject is notified that they are free to discontinue from the study at any time;
- Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided;
- Ensure each subject 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 subject; and
- Ensure that any incentives for subjects who participate in the study, as well as any provisions for subjects harmed as a consequence of study participation, are described in the Informed Consent Form that is approved by an Ethics Committee.

10.5 Changes to the protocol and Informed Consent Form

Study procedures will not be changed without the mutual agreement of the Principal Investigator and AstraZeneca.

If there are any substantial changes to the Clinical Study Protocol, then these changes will be documented in a Clinical Study Protocol amendment and, where required, in a new version of the Clinical Study Protocol (Revised Clinical Study Protocol).

The amendment is to be approved by the relevant Ethics Committee and, if applicable, also the national regulatory authority, 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 Principal Investigator(s). For distribution to Ethics Committees, see Section 10.3.

If a protocol amendment requires a change to a site's Informed Consent Form, AstraZeneca and the site's Ethics Committee 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 Ethics Committee.

10.6 Audits and inspections

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

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Appendix A Additional Safety Information

Further Guidance on the Definition of a Serious Adverse Event (SAE)

Life-threatening

'Life-threatening' means that the subject was at immediate risk of death from the adverse event 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 adverse event occurred in a more severe form, it might have caused death (e.g., hepatitis that resolved without hepatic failure).

Hospitalization

Outpatient treatment in an emergency room is not in itself an SAE, although the reasons for it may be (e.g., bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered adverse events 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 judgment should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalization, disability, or incapacity, but may jeopardize the subject or may require medical intervention to prevent 1 or more outcomes listed in the definition of serious. These should usually be considered as serious.

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

- Angioedema not severe enough to require intubation but requiring intravenous hydrocortisone treatment;
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine;
- Intensive treatment in an emergency room or at home for allergic bronchospasm;
- Blood dyscrasias (e.g., neutropenia or anemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalization; or
- 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 adverse event may have been caused by the drug.

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

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

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

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related.'

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

Appendix B International Airline Transportation Association (IATA) 6.2 Guidance Document

Labeling and shipment of biohazard samples

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories. For transport purposes, the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations 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, or life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are (e.g., Ebola, Lassa fever virus):

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

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens include, Hepatitis A, B, C, D, and E viruses, and human immunodeficiency virus types 1 and 2. They are assigned the following UN number and proper shipping name:

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

Exempt - all other materials with minimal risk of containing pathogens:

- Clinical study samples will fall into Category B or exempt under IATA regulations;
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging;
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content;
- IATA compliant courier and packaging materials should be used for packing and transportation, and packing should be done by an IATA certified person, as applicable; and
- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging/containment

materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Appendix C Pharmacogenetics Research

Background and Rationale

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

Genetic Research Plan and Procedures

Selection of genetic research population

See the Inclusion and Exclusion criteria in Section 3.

Discontinuation of subjects from this genetic research

Withdrawal of consent for genetic research: procedures for discontinuation are outlined in Section 3.9 of the main Clinical Study Protocol.

Collection of samples for genetic research

The blood sample for genetic research will be obtained from the subjects at Visit 2. Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding subjects who may withdraw due to an adverse event; such subjects would be important to include in any genetic analysis. If for any reason the sample is not drawn at Visit 2, it may be taken at any visit until the last study visit. Only 1 sample should be collected per subject for genetics during the study. Samples will be collected, labeled, stored, and shipped as detailed in the laboratory manual.

For blood volume, see Section 5.7 of the Clinical Study Protocol.

Coding and storage of DNA samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain subject confidentiality. Samples will be stored for a maximum of 15 years, from the end of the study, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

For all samples, irrespective of the type of coding used, the DNA will be extracted from the blood sample. The DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated contract laboratory. No personal details identifying the individual will be available to any person (AstraZeneca Representative employee or contract laboratory staff working with the DNA).

The samples and data for genetic analysis in this study will be single coded. The link between the subject enrollment/randomization code and the DNA number will be maintained and stored in a secure environment, with restricted access WITHIN the Clinical Genotyping Group Laboratory Information Management System (LIMS) at AstraZeneca. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and trace samples for destruction in the case of withdrawal of consent.

Ethical and Regulatory Requirements

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Section 10 of the main Clinical Study Protocol.

Subject data protection

AstraZeneca will not provide individual genotype results to subjects, any insurance company, any employer, their family members, general physician, or any other third party, unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, an AstraZeneca Physician or an Investigator might know a subject's identity and also have access to her genetic data. Also, Regulatory Authorities may require access to the relevant files, though the subject's medical information and the genetic files would remain physically separate.

Data management

Any genotype data generated in this study will be stored in the AstraZeneca genotyping LIMS database, or other appropriate secure system within AstraZeneca and/or third party contracted to work with AstraZeneca to analyze the samples.

The results from this genetic research may be reported in the Clinical Study Report for the main study, or in a separate report as appropriate.

Genotype data will be transferred to the clinical database, and merged with the clinical data from the main study, prior to the statistical analysis and reporting of the study.

Statistical Methods and Determination of Sample Size

The number of subjects that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A Statistical Analysis Plan will be prepared where appropriate.

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

Introduction

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries. Specific guidance on the managing liver abnormalities can be found in Section 6.3.7 of the Clinical Study Protocol.

During the course of the study, the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a subject meets potential Hy's Law criteria at any point during the study.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting potential Hy's Law criteria to agree whether Hy's Law criteria are met. Hy's Law criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than drug induced liver injury caused by the investigational medicinal product.

The Investigator is responsible for recording data pertaining to potential Hy's Law/Hy's Law cases and for reporting adverse events and serious adverse event (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

Definitions

Potential Hy's Law

Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3 × upper limit of normal (ULN) **together with** total bilirubin (TBL) ≥ 2 × ULN at any point during the study following the start of study medication irrespective of an increase in alkaline phosphatase (ALP).

Hy's Law

AST or ALT ≥ 3 × ULN **together with** TBL ≥ 2 × ULN, where no other reason, other than the investigational medicinal product, can be found to explain the combination of increases, (e.g., elevated ALP indicating cholestasis, viral hepatitis, another drug).

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

Identification of Potential Hy's Law Cases

In order to identify cases of potential Hy's Law, it is important to perform a comprehensive review of laboratory data for any subject who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 × ULN,
- AST ≥ 3 × ULN, or
- TBL ≥ 2 × ULN.

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

- Notify the AstraZeneca Representative,
- Determine whether the subject meets potential Hy's Law criteria (see Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits, and
- Promptly enter the laboratory data into the laboratory electronic case report form (eCRF).

Follow-up

Potential Hy's Law Criteria not met

If the subject does not meet potential Hy's Law criteria, the Investigator will:

- 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 subject meets potential Hy's Law criteria, the Investigator will:

- Notify the AstraZeneca Representative who will then inform the central study team.

The Study Physician contacts the Investigator to provide guidance and to discuss and agree on an approach for the study subjects' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the subject 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;

- Complete the 3 Liver eCRF modules as information becomes available; and

- If at any time (in consultation with the AstraZeneca Representative Study Physician) the potential Hy's Law case meets serious criteria, report it as a 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 potential Hy's Law criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the AstraZeneca Representative Study Physician will contact the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting potential Hy's Law criteria other than drug-induced liver injury caused by the investigational medicinal product. 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 adverse event will be made, and subsequently, whether the adverse event meets the criteria for an SAE:

- If the alternative explanation is not an adverse event, record the alternative explanation on the appropriate eCRF; or

- If the alternative explanation is an adverse event/SAE, record the adverse event/SAE in the eCRF accordingly and follow the AstraZeneca standard processes.

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

- 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, and

– As there is no alternative explanation for the Hy's Law 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 Hy's Law, 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 Hy's Law 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 subjects with liver metastases who meet potential Hy's Law criteria on study treatment, having previously met potential Hy's Law criteria at a study visit prior to starting study treatment.

At the first on-study treatment occurrence of potential Hy's Law criteria being met the Investigator will:

- Determine if there has been a significant change in the subjects' condition* compared with the last visit where potential Hy's Law criteria were met*:

– If there is no significant change, no action is required; or

– If there is a significant change, notify the AstraZeneca Representative, who will inform the central study team, then follow the subsequent process described in "Potential Hy's Law Criteria met" of this Appendix.

* A 'significant' change in the subject's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or TBL) 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 subject meets potential Hy's Law criteria on study treatment and has already met potential Hy's Law criteria at a previous on-study treatment visit.

The requirement to conduct follow-up, review, and assessment of a repeat occurrence(s) of potential Hy's Law 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 potential Hy's Law criteria being met and answer the following question:

- Was the alternative cause for the previous occurrence of potential Hy's Law criteria being met found to be the disease under study e.g., chronic or progressing malignant disease, severe infection, or liver disease, or did the subject meet potential Hy's Law criteria prior to starting study treatment and at their first on study treatment visit as described in "Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment?"

If No: follow the process described in "Potential Hy's Law Criteria met" of this Appendix.

If Yes: Determine if there has been a significant change in the subject's condition* compared with when potential Hy's Law criteria were previously met:

- If there is no significant change, no action is required; or
- If there is a significant change, follow the process described in this Appendix.

* A 'significant' change in the subject's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or TBL) 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

Food and Drug Administration 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 Acceptable Birth Control Methods

Olaparib is regarded as a compound with medium/high fetal risk.

- Women of childbearing potential and their partners, who are sexually active, must agree to the use of 2 highly effective forms of contraception in combination (as listed below). This should be started from the signing of informed consent and continue throughout the period of taking study treatment and for at least 1 month after last dose of study medication, or they must totally/truly abstain from any form of sexual intercourse (see below).

Acceptable non-hormonal birth control methods include:

- Total/True abstinence: When the subject refrains from any form of sexual intercourse and this is in line with their usual and/or preferred lifestyle; this must continue for the total duration of the trial and for at least 1 month after the last dose of study drug. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods, or declaration of abstinence solely for the duration of a trial) and withdrawal are not acceptable methods of contraception;

- Vasectomized sexual partner PLUS male condom. With participant assurance that partner received post-vasectomy confirmation of azoospermia;

- Tubal occlusion PLUS male condom; and/or

- Intrauterine device PLUS male condom. Provided coils are copper-banded.

Acceptable hormonal methods:

- Normal and low-dose combined oral pills PLUS male condom;

- Cerazette (desogestrel) PLUS male condom. Cerazette is currently the only highly efficacious progesterone-based pill;

- Hormonal shot or injection (e.g., Depo-Provera) PLUS male condom;

- Etonogestrel implants (e.g., Implanon, Norplant) PLUS male condom;

- Norelgestromin/ethinyl estradiol transdermal system PLUS male condom;

- Intrauterine system device (e.g., levonorgestrel releasing Intrauterine system-Mirena®) PLUS male condom; and/or
- Intravaginal device (e.g., ethinyl estradiol and etonogestrel) PLUS male condom.

Appendix F Eastern Cooperative Oncology Group (ECOG) Performance Status

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol.:
Oken, MM, Creech, RH, Tormey, DC, Horton, J, Davis, TE, McFadden, ET, et al.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-655.

Appendix G Response Evaluation Criteria in Solid Tumors Guidelines (version 1.1)

Measurability of Tumor at Baseline

Definitions

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

Measurable

Tumor lesions: Must be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by computed tomography (CT) scan (CT scan slice thickness no greater than 5 mm);
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable); or
- 20 mm by chest X-ray.

Measurable malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline (i.e., screening for this study) and in follow-up (i.e., all measurements past screening for this study), only the short axis will be measured and followed. See also notes below on "Baseline documentation of target and non-targeted lesions (TLs)" for information on lymph node measurement.

Non-measurable

All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, and abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Special Considerations Regarding Lesion Measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment.

Bone Lesions

- Bone scan, positron emission tomography scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or magnetic resonance imaging (MRI) can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic Lesions

- Lesions that meet the criteria for radiographically-defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- "Cystic lesions" thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as TLs.

Lesions with Prior Local Treatment

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are not considered measurable unless there has been demonstrated progression in the lesion.

Specifications by Methods of Measurements

Measurement of Lesions

All measurements should be recorded in metric notation, using calipers, if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and NEVER more than 4 weeks before the beginning of the treatment.

Method of Assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation should always be performed rather than clinical examination unless the lesion(s) being followed cannot be imaged but is assessable by clinical exam.

Computed tomography, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. An MRI is also acceptable in certain situations (e.g., for body scans).

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a subject to be considered in complete response.

Tumor Response Evaluation

Assessment of Overall Tumor Burden and Measurable Disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements.

Baseline Documentation of "Target" and "Non-target" Lesions

When more than 1 measurable lesion is present at baseline, all lesions up to a maximum of 5 lesions total (representative of all involved organs) should be identified as target lesions (TLs) and will be recorded and measured at baseline (this means in instances where subjects have only 1 or 2 organ sites involved, a maximum of 2 and 4 lesions, respectively, will be recorded).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), should be representative of all involved organs, 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.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. As noted above, pathological nodes which are defined as measurable and may be identified as TLs must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as 2 dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm × 30 mm has a

short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-TLs. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all TLs will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then, as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease), including pathological lymph nodes, should be identified as non-TLs and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present," "absent," or in rare cases "unequivocal progression." In addition, it is possible to record multiple non-TLs involving the same organ as a single item on the case record form (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

Response Criteria

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all TLs. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of TLs, taking as reference the baseline sum diameters.

Progressive 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. (Note: The appearance of 1 or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Special Notes on the Assessment of Target Lesions

Lymph nodes: Lymph nodes identified as TLs should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as TLs, the "sum" of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. For PR, SD, and PD, the actual short axis measurement of the nodes is to be included in the sum of TLs.

Target lesions that become "too small to measure": While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes which are recorded as TLs at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being "too small to measure." When this occurs, it is important that a value be recorded in the electronic case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible; therefore, providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment: When non-nodal lesions "fragment," the longest diameters of the fragmented portions should be added together to calculate the TL sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the "coalesced lesion."

Evaluation of Non-target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-TLs. While some non-TLs may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the Clinical Study Protocol.

CR: Disappearance of all non-TLs and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-CR/Non-PD: Persistence of 1 or more non-TL(s) and/or maintenance of tumor marker level above the normal limits.

PD: Unequivocal progression (see comments below) of existing non-TLs (Note: The appearance of 1 or more new lesions is also considered progression).

Special Notes on Assessment of Progression of Non-target Disease

The concept of progression of non-target disease requires additional explanation as follows, when the subject also has measurable disease. In this setting, to achieve "unequivocal progression" on the basis of the 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 1 or more non-TLs is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e., not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the subject's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the subject who has visceral disease at baseline and while on study has a CT or MRI brain scan ordered which reveals metastases. The subject's brain metastases are considered to be evidence of PD, even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment. No confirmatory measurement for CR, PR, or SD is required in the study.

The subject's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

Time Point Response

It is assumed that at each protocol-specified time point, a response assessment will occur. Table 14 provides a summary of the overall response status calculation at each time point for subjects who have measurable disease at baseline.

Table 14 Time Point Response: Subjects with Target (± Non-target) Disease

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	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, and NE = inevaluable.

Missing Assessments and Inevaluable Designation

When no imaging/measurement is performed at all at a particular time point, the subject is not evaluable at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluable at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a subject had a baseline sum of 50 mm with 3 measured lesions and at follow-up only 2 lesions were assessed, but those gave a sum of 80 mm, the subject will have achieved PD status, regardless of the contribution of the missing lesion.

Best Overall Response: All Time Points

The best overall response is determined once all the data for the subject is known.

Best response determination in studies where confirmation of CR or PR IS NOT required:
Best response in these studies is defined as the best response across all time points (e.g., a subject who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the Clinical Study Protocol-specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the subject's best response depends on the subsequent assessments. For example, a subject who has SD at first assessment, PD at second, and does not meet minimum duration for SD, will have a best

response of PD. The same subject lost to follow-up after the first SD assessment would be considered inevaluable.

Best response determination in trials where confirmation of complete or partial response IS required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the Clinical Study Protocol. In this circumstance, the best overall response can be interpreted as in Table 15.

Table 15 Best Overall Response When Confirmation of CR and PR is Required

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

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

Special Notes on Response Assessment

When nodal disease is included in the sum of TLs and the nodes decrease to "normal" size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal, in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that subjects with CR may not have a total sum of "zero" in the electronic case report form.

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such subjects is to be determined by evaluation of target and non-target disease.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Source: Eisenhauera EA, Therasseb P, Bogaertsc J, Schwartzd LH, Sargente D, Ford R, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer. 2009;45:228-247.

Appendix H Gynecological Cancer Intergroup (GCIG) Guidelines

For definitions for response and progression agreed by the GCIG, see Rustin GJS, Vergote I, Eisenhauer E, Pujade-Lauraine E, Quinn M, Thigpen T, et al. Definitions for response and progression in ovarian cancer clinical trials incorporating RECIST 1.1 and CA-125 agreed by the Gynecological Cancer Intergroup (GCIG). Intl J Gynecol Cancer. 2011;21:419-423.

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