Statistical Analysis Plan

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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

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Study Statistician

03 OCT 2019
Date

Medical Monitor

30 OCT 2019
Date

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Global Product Statistician PPD

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Study Statistician

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Global Product Statistician

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse event
AESI	Adverse event of special interest
AML	Acute myeloid leukemia
APTT	Activated partial thromboplastin time
ATC	Anatomic therapeutic class
BMI	Body mass index
BoR	Best objective response
BRCAm	BRCA mutation
BRCAwt	BRCA wild type
CA-125	Cancer antigen 125
CA-125 RR	Cancer antigen 125 Response Rate
CI	Confidence interval
CR	Complete response
CRF	Case report form
CSR	Clinical study report
DCR	Disease control rate
DoR	Duration of response
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
gBRCAm	Germline BRCA mutation
gBRCAwt	Germline BRCA wild type
GCIG	Gynecological Cancer Intergroup
HRD	Homologous recombination deficiency
HRRm	Homologous recombination repair mutation
INR	International Normalized Ratio
MedDRA	Medical Dictionary for Regulatory Activities
MDS	Myelodysplastic syndrome
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Event
NE	Not evaluable

Abbreviation or special term	Explanation
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
PT	Preferred term
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumors
sBRCAm	Somatic BRCA mutation
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SOC	System organ class
STD	Standard deviation
TEAE	Treatment-emergent adverse event
TL	Target lesion
TTAP	Time to any progression
ULN	Upper limit of normal
WHO	World Health Organization

AMENDMENT HISTORY

Date	Brief description of change
8 January 2018	Initial Version
3 October 2019	Version 2.0. Updated language pertaining to coding of medical history, cancer therapies, Full Analysis Set, and determination of Adverse Events of Special Interest. Added language pertaining to safety summaries. Added language to define HRRm positive population and summary descriptions for Myriad gene panels. Visit window definitions added for applicable by visit summaries.

1. STUDY DETAILS

This section outlines basic details of the study including the objectives, design aspects, and number of subjects to be included.

1.1 Study Objectives

The primary, secondary, safety, and exploratory objectives of the study are as follows:

Table 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 Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria (Investigator determined).	• The objective response rate (ORR), defined as the percentage of subjects with a best overall response of confirmed complete response (CR) or partial response (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 and the Full Analysis Set (in a sensitivity analysis if the populations are different).

The four cohorts to be included are:

- Cohort 1: germline BRCA mutation (gBRCAm)
- Cohort 2: somatic BRCA mutation (sBRCAm) and germline BRCA wild type (gBRCAwt)
- Cohort 3: myChoice® homologous recombination deficiency (HRD) positive (genomic instability positive) and BRCAwt (no BRCA mutation)
- Cohort 4: myChoice® HRD negative (genomic instability negative) and BRCAwt (no BRCA mutation)

Table 2: Secondary Objectives

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) • Overall survival (OS) • 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 progression. • CA-125 response rate (CA-125 RR), defined as the percentage of subjects with a CA-125 response according to Gynecological Cancer Intergroup (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 disease 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).

Table 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 (AEs), including serious adverse events (SAEs); physical examination; vital signs including blood pressure, pulse, and electrocardiogram; and collection of clinical chemistry/hematology parameters.

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1.2 Study Design

This Phase II, open-label, non-randomized, multi-center cohort study will assess the efficacy (ORRs) and safety of olaparib monotherapy in 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 a HRD tumor assessed via the myChoice® HRD tumor test, or have wild type tumor type (BRCA and HRD).

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

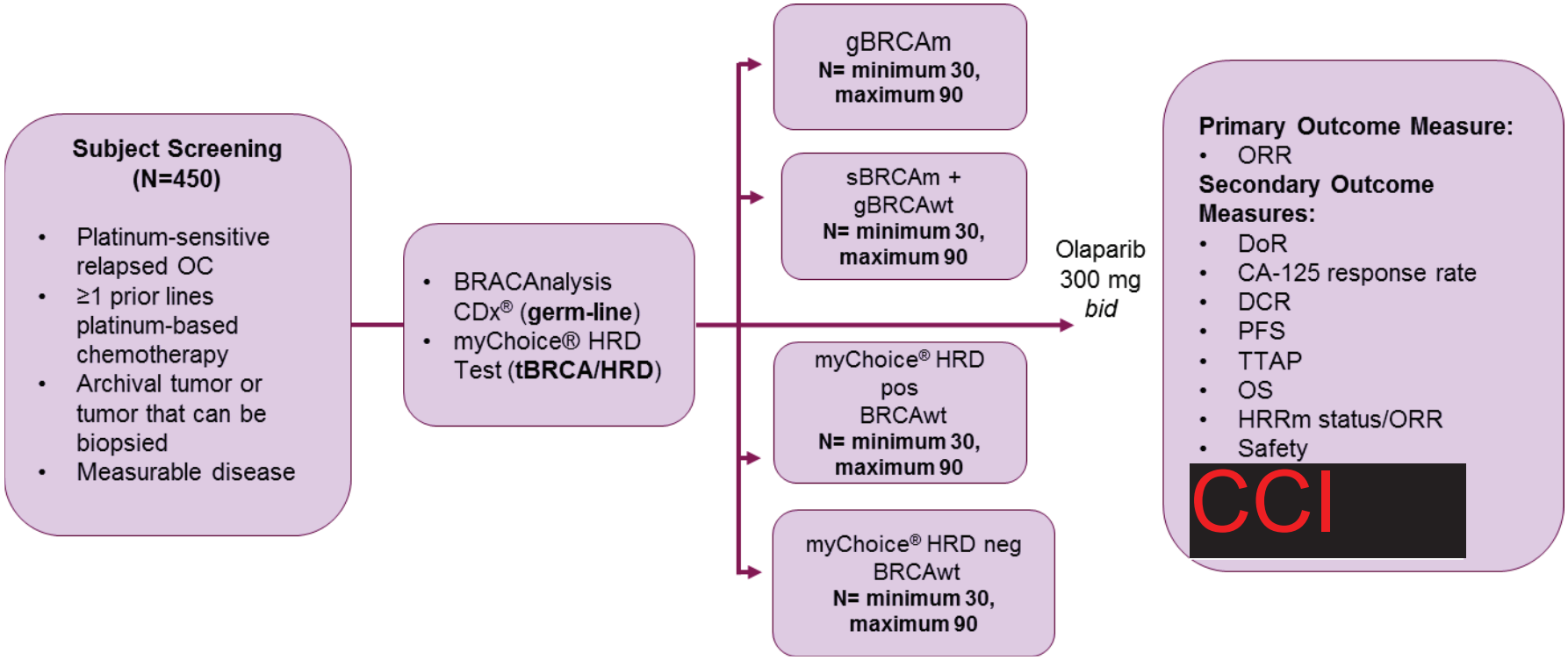
point the cohort will be closed to further enrollment. Once all 4 cohorts have at least 30 subjects (unless early stopping criteria are met), the study will be closed to further enrollment. All subjects enrolled will receive olaparib tablets 300 mg (two 150 mg tablets) orally bid, in 4 week cycles (i.e., a new bottle will be dispensed every 4 weeks) in the active treatment period of the study.

Subjects will continue treatment with olaparib tablets 300 mg (two 150 mg tablets), bid, from enrollment (Visit 2) until objective radiological disease progression as per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 as assessed by the Investigator, or when they meet any discontinuation criteria (see Study Protocol 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 or email contact with the subject, subject's family, or by contact with the subject's current physician.

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.

See Figure 1 below for the diagram of the study. The Study Plan for the study is provided in the Study Protocol Table 6.

Figure 1 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).

1.3 Number of Subjects

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%.

2. ANALYSIS SETS

2.1 Definition of Analysis Sets

- **Full Analysis Set**: comprises all subjects entered (including those who did not receive treatment but excludes screening failures).
- **Efficacy Analysis Set:** comprises all subjects who received at least 1 dose of olaparib and had a baseline tumor assessment indicating measurable disease.
- **Safety Analysis Set:** comprises all subjects who received at least 1 dose of olaparib.

Table 6 provides a summary of outcome variables and analysis populations in the study.

Table 6: Summary of Outcome Variables and Analysis Populations

Outcome Variable	Population
Efficacy Data	
- Primary endpoint: ORR	Efficacy, Full[b]
- Secondary endpoints: DoR, CA-125 RR[a], DCR, PFS, TTAP, OS, HRRm	Efficacy, Full[b]
Safety Data	
- Demography	Full, Safety[b], Efficacy[b]
- AEs	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).
b. Analysis set only to be used in tables and figures if the populations are different.

CA = Cancer antigen; 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.

Efficacy analyses will be based primarily on the Efficacy Analysis Set while the Full Analysis Set will be used only for a sensitivity analysis in the case that the two populations are different.

2.2 Violations and Deviations

A per-protocol analysis excluding subjects with specific important protocol deviations is not planned for this study.

Study deviations determined from the electronic case report form (CRF) module for inclusion/exclusion criteria will be listed. Any other deviations from monitoring notes or reports will be reported in an appendix in the clinical study report (CSR).

3. STUDY OUTCOME VARIABLES

This section describes the variables collected and derived for analysis of the primary, secondary, exploratory, and safety endpoints of the study. Data collection of these variables will occur at the times outlined in the Study Plan (see Study Protocol Table 6).

3.1 Primary Outcome Variable

The primary outcome variable for this study is the ORR, defined as the percentage of subjects with measurable disease with at least 1 visit response of CR or PR (at any time up to and including the defined analysis cut-off point) that is confirmed at least 4 weeks later.

Tumor response will be assessed by the Investigator according to RECIST v1.1 criteria (see Section 3.3.1). 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 with a baseline assessment and all post-baseline tumor assessments of not evaluable (NE) will be included in the denominator of the response rate calculation.

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 progressive disease (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.

3.2 Secondary Outcome Variables

The secondary outcome variables considered in this study are DoR, CA-125 RR, DCR, PFS, TTAP (by RECIST, CA-125 or death), OS, and the relation of HRRm status to clinical outcomes.

3.2.1 Duration of Response

The DoR is 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 time of the initial response will be defined as the latest of the dates contributing towards the first visit response of PR or CR. The end of response should coincide with the date of PD or death from any cause used for the PFS secondary endpoint. If a subject does not progress following response, then the subject's DoR will use the PFS censoring time as defined in Section 3.2.4.

If the response is not confirmed (per RECIST v1.1 Investigator's assessment), the response will not be included.

3.2.2 CA-125 Response Rate

The CA-125 RR is defined as the percentage of CA-125 evaluable subjects achieving a CA-125 response (see Section 3.3.2). Additionally, 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 RR will be analyzed on a subset of the analysis set/s (i.e., excluding subjects whose baseline CA-125 level is not ≥ 2 × upper limit of normal (ULN) and/or not assessed within 2 weeks of starting treatment with olaparib).

3.2.3 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, prior to any PD event.

3.2.4 Progression-Free Survival

The PFS will be 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 anti-cancer therapy prior to disease progression.

Objective radiological progression is defined as at least a 20% increase in the sum of the diameters of the target lesions (TLs) (compared to previous minimum sum) and an absolute increase of > 5 mm, an overall non-TL assessment of progression, or a new lesion.

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 prior to the two missed visits.

Given the scheduled tumor assessment scheme (i.e., every 8 weeks for the first 48 weeks and every 12 weeks thereafter), the definition of 2 missed visits will change:

- If the previous RECIST assessment is less than study Day 274 (i.e. week 39), then 2 missing visits will equate to 18 weeks since the previous RECIST assessment, allowing for early and late visits (i.e. 2 x 8 weeks + 1 week for an early assessment + 1 week for a late assessment).

- If the previous RECIST assessment is between Week 39 and Week 49 (the missing visits occur during the transition from 8-weekly to 12-weekly assessments), then two missing visits will equate to 22 weeks (i.e., take the average of 8 and 12 weeks which gives 10 weeks and then apply same rationale, 2 x 10 weeks + 1 week for an early assessment + 1 week for a late assessment).

- If the previous RECIST assessment is after Day 344 (i.e. week 49), two missing visits will equate to 26 weeks (i.e., 2 x 12 weeks + 1 week for an early assessment + 1 week for a late assessment).

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.

3.2.5 Time to Earliest Progression by RECIST or CA-125, or Death

The TTAP 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.

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 (see Section 3.3.2).

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. Since CA-125 is assessed more frequently than RECIST, the two missed visits rule is based upon the RECIST schedule. Therefore, if a subject dies, has RECIST progression or has CA-125 progression after two or more missed RECIST assessments, the subject will be censored at the last evaluable RECIST assessment prior to the two missed visits.

3.2.6 Overall Survival

OS 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 the primary endpoint 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.

Note, in the absence of survival calls being made, it may be necessary to use all relevant CRF fields to determine the last recorded date on which the subject is known to be alive for those subjects still on treatment. The last date known to be alive for each individual subject is defined as the latest among the following dates recorded on the CRF:

- AE start and stop dates
- Study treatment start and stop dates
- Laboratory assessment dates
- Dates of vital signs, physical exam, Eastern Cooperative Oncology Group (ECOG) performance status, and electrocardiogram (ECG) assessments
- Disease assessment dates
- Start and stop dates of concomitant medications including transfusions, procedures, and alternative anti-cancer therapy
- Date of last known alive on survival status

3.2.7 HRRm Status

Subjects in the 2 BRCAwt cohorts (3 and 4) will have their HRRm status tested (by HRRm gene panel) 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) and by cohort within HRRm status.

Assignment of HRRm status will be based on results of detection of deleterious/suspected deleterious mutation in one or more of the following genes in the Myriad HRRm gene panel assay: ATM, RAD51B, RAD51C, RAD54L, RAD51D, FANCJ/BRIP1, FANCL, FANCN (PALB2), BARD1, CHEK1, CHEK2, CDK12, PPP2R2A.

Subjects with valid HRRm gene panel assay test result but with no deleterious/suspected deleterious mutation detected in above genes will be considered HRRm negative.

Subjects with invalid or missing HRRm gene panel assay results will be considered missing.

3.3 Calculation or Derivation of Efficacy Variables

3.3.1 RECIST Assessments

At each visit (both scheduled and unscheduled), subjects will be assigned a visit response of CR, PR, SD, PD, or NE based on RECIST v1.1 guidelines based on the Investigator's assessment. The overall visit response will be derived by the Investigator using the information from the TLs, NTLs and new lesions. There will be no programmatic rederivation of visit responses based on eCRF data for the primary assessment of overall response and only the Investigator's assessment will be used. Programmatic derivations of visit responses based on TLs, NTLs and new lesions may be performed, if considered required as a sensitivity analysis.

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 first dose) 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.

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).

A confirmed response of PR/CR means that a response of PR/CR is recorded at 1 visit (Investigator assessed) and confirmed by repeat imaging not less than 4 weeks after the visit when the response was first observed and with no evidence of progression between the initial and PR/CR confirmation visit.

3.3.2 CA-125 Assessments

The CA-125 response or progression 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 is considered to have 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 are considered evaluable for CA-125 response if and 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 will be classified as CA-125 complete responders.

Progression 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
- 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

CA-125 progression will be assigned the date of the first measurement that meets the criteria above. Subjects are not evaluable for CA-125 assessments 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 during the previous 28 days.

3.4 Safety Outcome Variables

Safety and tolerability of olaparib will be assessed in terms of AEs, SAEs, Adverse Events of Special Interest (AESIs), AEs leading to discontinuation, deaths, laboratory assessments (e.g., clinical chemistry, hematology, coagulation, and urinalysis), electrocardiograms, physical examinations, vital signs, and ECOG performance status. Definitions and descriptions of these events can be found in the following subsections. Safety assessments will be performed at the times described in the Study Plan (see Study Protocol Table 6). Reporting of safety-related events will end 30 days after the last dose of olaparib. If olaparib treatment remains ongoing at the end of the study, safety reporting will continue until 30 days after the last dose of olaparib.

3.4.1 Adverse Events

An AE 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 AE can include an undesirable medical condition occurring at any time, even if no treatment has been started (e.g. procedure-related condition).

AEs 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. The reporting period for AEs will terminate 30 days after the final dose of olaparib is taken.

The grading scales found in the revised National Cancer Institute Common Terminology Criteria for Adverse Event (NCI-CTCAE) v4.03 will be utilized for all events with an assigned CTCAE grading. If a CTCAE grade is not given it will not be imputed. AEs will be coded and classified by system organ class (SOC) and preferred term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA, v19.0 or later).

For each episode of an AE, all changes to the CTCAE grade attained, as well as the highest attained CTCAE grade, should be recorded. The assessment by the Investigator regarding the relationship between olaparib and the AE will also be recorded.

3.4.1.1 Adverse Events of Special Interest

AESIs 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 AESIs for olaparib include the following:

- Myelodysplastic syndrome (MDS) / Acute Myeloid Leukemia (AML)
- New primary malignancy (other than MDS/AML)
- Pneumonitis

3.4.2 Clinical Laboratory Evaluations

Blood and urine samples for determination of clinical chemistry, hematology, coagulation, and urinalysis parameters will be collected at the times indicated in the Study Plan (see Study Protocol Table 6). Additional safety samples may be collected if clinically indicated the discretion of the Investigator. The date, time of collection, and results will be recorded. Both scheduled and unscheduled visits will be included for analyses.

The laboratory parameters to be collected are listed in Table 7 below.

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.

3.4.2.1 Coagulation Panel

Coagulation tests are not required and will be collected only if clinically indicated. Coagulation parameters may include activated partial thromboplastin time (APTT) or International normalized ratio (INR), unless the subject is receiving warfarin (subjects receiving warfarin are permitted to participate in the study).

Each coagulation test result will be recorded.

3.4.3 Vital Signs

Vital signs measurements will be collected at the times indicated in the Study Plan (see Study Protocol Table 6) and includes systolic and diastolic blood pressure, respiratory rate, pulse rate, and body temperature. Height will be assessed at screening only. Weight and body temperature will be assessed at screening and as clinically indicated, according to the times indicated in the Study Plan.

Systolic and diastolic blood pressure (mmHg) and pulse rate (beats/min) will be measured at the times indicated in the Study Plan with an appropriate cuff size after 10 minutes rest.

Body temperature will be measured in degrees Celsius.

Any changes in vital signs will be recorded as an AE, if applicable. If classified as an AE, the corresponding information will be collected and recorded.

3.4.4 Electrocardiograms

ECGs will be obtained at the times indicated in the Study Plan (see Study Protocol Table 6). Twelve-lead ECGs will be obtained after the subject has rested in a supine position for at least

5 minutes in each case. 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, it will be classified as an AE and the data collection and recording procedures for AEs will be followed.

3.4.5 Physical Examination

Physical examinations will be performed at the times indicated in Study Plan (see Study Protocol Table 6).

The physical examination will include 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.

After the baseline assessment the details of the physical examination will not be directly recorded unless in relation to an AE/SAE.

3.4.6 Other Safety Variables

Bone marrow or blood cytogenetic samples may be collected for subjects with prolonged hematological toxicities (see Study Protocol Section 6.7.1).

Other tests (e.g. serum or urine beta-human chorionic gonadotropin pregnancy test) will be recorded as indicated in the Study Plan (see Study Protocol Table 6).

3.4.7 Exposure and Relative Dose Intensity

During the treatment period, subjects will continue with olaparib tablets 300 mg (two 150 mg tablets), *bid*, 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.

Total exposure to study treatment:

- Total exposure (days) = date of last dose of study drug – date of first dose of study drug + 1

Relative dose intensity (RDI) is the percentage of actual dose delivered relative to the intended dose through to treatment discontinuation.

RDI will be calculated as follows:

- RDI (%) = 100 * d/D

where d is the actual cumulative dose delivered up to the actual last day of dosing (mg) and D is the intended cumulative dose up to the actual last day of dosing (mg). D is the total dose that would be delivered, if there were no modification to dose or schedule.

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4. ANALYSIS METHODS

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.

4.1 General Principles

The statistical analyses for efficacy and safety data will be performed by Medpace Inc.

The analyses of the data collected within this study will be descriptive only, with no formal statistical testing. Statistical analyses will be performed in SAS® v9.3 or higher.

All analyses will be presented by cohort. Additionally, efficacy analyses in the 2 BRCAwt cohorts (3 and 4) will also be presented according to HRRm status (denoted HRRm positive and HRRm negative).

Efficacy analyses will be performed using the Efficacy Analysis Set and the Full Analysis Set (in a sensitivity analysis if the populations are different).

Safety analyses and exploratory analyses will be performed using the Safety Analysis Set.

Demography and baseline characteristics data will be summarized based on the Full Analysis Set, Safety Analysis Set, and Efficacy Analysis Set. If the populations are identical to each other, they will be presented only once for the Full Analysis Set.

By-subject listings will be presented based on the Full Analysis Set.

4.1.1 Baseline and Data Consideration

Unless otherwise specified, baseline is defined as the last non-missing value taken before the first dose of olaparib for all study variables.

Study Day 1 will be considered as the date of the first dose of olaparib.

Unscheduled visits will be considered for derivation of minimum and maximum post-baseline values.

To allow for any presentations that summarize values by visit, visit windows will be defined according to Table 8 below. The upper limit of the interval falls half way between the two visits (the lower limit of the first post-baseline visit will be Day 2). The half way point is assumed to be the midpoint of the number of days between the visits, excluding both visit days. If an odd number of days exist between two consecutive visits then the upper limit is taken as the midpoint value plus 0.5 day.

If there is more than one value per patient within a time window then the closest value will be summarized, or the earlier value in the event the values are equidistant from the nominal visit day.

Table 8: Visit Window Definition

Visit	Day	Laboratory Assessments
Screening	Up to Day 1	Day -28 to -1
Day 1	Day 1	Day 1
Day 8	Day 8	Day 2 to Day 11
Day 15	Day 15	Day 12 to Day 18
Day 22	Day 22	Day 19 to Day 25
Day 29	Day 29	Day 26 to Day 43
Day 57	Day 57	Day 44 to Day 71
Day 85	Day 85	Day 72 to Day 99
Day 113	Day 113	Day 100 to Day 127
Day 141	Day 141	Day 128 to Day 155
Day 169	Day 169	Day 156 to day 183
Day 197	Day 197	Day 184 to Day 211
Day 225	Day 225	Day 212 to Day 239
Day 253	Day 253	Day 240 to Day 267
Day 281	Day 281	Day 268 to Day 295
Day 309	Day 309	Day 296 to Day 323
Day 337	Day 337	Day 324 to Day 351
Day 365	Day 365	Day 352 to Day 407
Day 449	Day 449	Day 408 to Day 491

Day 533	Day 533	Day 492 to Day 575
Day 617	Day 617	Day 576 to Day 659
Day 701	Day 701	Day 660 to Day 743
Etc.		

For subsequent visits extending beyond Day 701, additional visit windows will be defined in the same manner.

4.1.2 Covariate Adjustment

Adjustment for covariates is not applicable for the planned descriptive analysis.

4.1.3 Multicenter Studies

No adjustments will be made for multiple study centers.

4.1.4 Multiple Comparisons

No adjustments for multiple comparisons will be made for the planned descriptive analysis.

4.1.5 Missing Data

Unrecorded data values will be recorded as missing. Only recorded (i.e. complete) data values will be used for statistical analyses. In general, invalid or missing values will not be imputed unless otherwise stated.

To be conservative in reporting treatment-emergent adverse events (TEAEs), when an AE is proven to occur prior to the first dose of study drug, it is considered as a non-treatment-emergent event. Otherwise, it is considered to be a TEAE. Therefore, if the start date of an AE is missing but the stop date is either overlapping into the treatment period or missing, the AE will be considered to be a TEAE, taking the worst-case approach. When partial dates are present in the data, both a partial start date and/or a partial stop date will be evaluated to determine whether it can be conclusively established that the AE started prior to the start of the study drug. If the above cannot be conclusively established based on the partial dates, then the AE will be considered as a TEAE. In addition, an AE that begins more than 30 days after the last dose of study drug will not be considered as TEAE unless it is related to the study drug.

Missing AE data, such as missing causality assessment (after data querying), will be assumed to be related to study drug.

For classification of prior and concomitant medications, medications missing both start and stop dates, or having a start date prior to the first dose of the study drug and missing the stop date, or having a stop date after the start of the study drug and missing the start date, will be

considered as concomitant medications. When partial dates exist in the data, the same logic to that of the AEs described above will be used.

Missing safety or exploratory data will generally not be imputed. However, safety assessment values of the form of "< x" (i.e., below the lower limit of quantification) or "> x" (i.e., above the upper limit of quantification) will be imputed as "x" in the calculation of summary statistics but displayed as "< x" or "> x" in the listings.

4.1.6 Examination of Subgroups

Exploratory subgroup analyses may be conducted to further describe the relationship between clinical outcomes and subject characteristics, including, but not limited to the number of lines of previous chemotherapy.

4.2 Analysis Methods

No formal statistical tests will be performed; the statistical analyses for primary, secondary, exploratory, and safety endpoints will be purely descriptive.

Unless otherwise specified, continuous variables will be summarized by the number of observations (n), mean, standard deviation (STD), median, Q1, Q3, minimum, and maximum. Categorical variables will be summarized by frequency counts and percentages for each category. Confidence intervals (CIs), when presented, will generally be constructed at the 2-sided 95% level.

4.2.1 Study Population Data

4.2.1.1 Subject Disposition

Subject disposition will be summarized for the Full Analysis Set. The following subject disposition categories will be summarized by cohort and overall:

- Subjects who were enrolled
- Subjects who were treated
- Subjects who discontinued from study treatment
- Subjects who discontinued from study

For subjects who discontinued from study treatment and subjects who discontinued from study, a summary will be provided which lists the reasons for discontinuation.

The number and percentage of subjects in each defined analysis population will also be tabulated.

All subject disposition data will be presented in a by-subject listing.

4.2.1.2 Protocol Deviations

All protocol deviations determined to be reportable in the CSR per the study Protocol Deviation Plan will be presented in a by-subject listing.

4.2.1.3 Demographic and Baseline Characteristics

Demographic characteristics including race, and ethnicity will be summarized with contingency tables. Age at informed consent (years), baseline height (cm), weight (kg), and body mass index (BMI) (kg/m^2) will be summarized with descriptive statistics.

Baseline disease characteristics will be collected during the Screening period. Time from diagnosis (months) will be summarized with summary statistics. Metastatic status, site of metastasis, primary tumor location, tumor grade, FIGO stage, baseline ECOG performance status, number of lines of prior cancer therapy, best response to last cancer therapy, prior radiotherapy, and HRRm status (for the 2 BRCAwt cohorts) will be summarized with contingency tables.

Demographic and baseline disease characteristic information will be presented in a by-subject listing.

4.2.1.4 Medical History

A complete medical and surgical history will be collected during the Screening period.

All reported medical history conditions and prior surgeries will be presented in a by-subject listing.

4.2.1.5 Prior and Concomitant Medications

Cancer therapies, prior medications, and concomitant medications will be coded using the World Health Organization Drug Dictionary Enhanced (WHO-DDE B2, September 2016 or later). Prior medications are medications used and stopped before the first dose of study drug. Concomitant medications are medications that were taken on or after the first dose of study drug.

Concomitant medications will be summarized by anatomic therapeutic class (ATC) and PT for the Safety Analysis Set. Although a subject may have taken two or more medications, the subject is counted only once within an ATC classification. The same subject may contribute to two or more preferred terms in the same classification. Prior medications and cancer therapies will be summarized in the same manner.

All prior and concomitant medications and cancer therapies will be presented in by-subject listings.

4.2.1.6 Exposure and Compliance

The total exposure to olaparib and the RDI will be summarized using descriptive statistics by cohort for the Safety Analysis Set. The number and percentage of cycles of olaparib initiated will be tabulated.

Additionally, the number and percentage of subjects with dose reduction, dose interruption, and dose modification will be presented along with the reasons for dose adjustment.

All study drug administration data will be presented in a by-subject listing.

4.2.2 Primary Analysis

The primary analysis will involve analysis of the ORR by cohort among subjects in the Efficacy Analysis Set and the Full Analysis Set (in a sensitivity analysis if the populations are different). The point estimate of the ORR along with the exact Clopper-Pearson 95% CI will be presented.

In addition to the analysis described above, best objective response (BoR) will be summarized descriptively by cohort to show the number and percentage of subjects in each response category. BoR will be calculated based on the overall visit responses from each RECIST assessment by the investigator. BoR is defined as the best response (in the order of CR, PR, SD, PD) a subject has had following the first dose of study treatment, but prior to and including RECIST progression or the last evaluable assessment in the absence of RECIST progression. CR or PR must be confirmed. For determination of a best response of SD, the earliest of the dates contributing towards a particular overall visit assessment will be used. SD should be recorded at least 8 weeks minus 1 week, i.e. at least 49 days (to allow for an early assessment within the assessment window), after first dose of study treatment. For CR/PR, the initial overall visit assessment that showed a response will use the latest of the dates contributing towards a particular overall visit assessment. Subjects with no evaluable RECIST assessments after first dose of study treatment will be assigned to the NE category (unless there is evidence of progression, in which case the response will be assigned as PD).

All tumor assessment data will be presented in by-subject listings.

4.2.3 Secondary Analyses

Secondary analyses will be based on the Efficacy Analysis Set and the Full Analysis Set (in a sensitivity analysis if the populations are different) or a subset of these populations (e.g. those subjects that have exhibited a radiologically confirmed response). Each analysis will be presented separately for each cohort and no comparisons between cohorts will be made.

4.2.3.1 Duration of Response

The Kaplan-Meier estimate of the median DoR and the Brookmeyer-Crowley 95% CI will be presented. Only subjects with a confirmed response will be included in this summary. Summaries will also be presented for the number and percentage of subjects experiencing

progression or death, and those who are censored. DoR at clinically relevant time points (e.g. 6, 12, 18 and 24 months) will also be summarized.

Kaplan-Meier plots of DoR will be presented. Swimmer plots that show the profile of each subject who responds will also be produced.

4.2.3.2 CA-125 Response Rate

The CA-125 RR and CA-125 CR rate will be analyzed based on subjects who are evaluable for CA-125 response (subjects with baseline CA-125 $\geq$ 2 x ULN and/or within 2 weeks prior to starting olaparib).

The CA-125 RR and CA-125 CR rate will be presented together with the exact Clopper-Pearson 95% CI for CA-125 response evaluable subjects.

In addition to the analysis described above, CA-125 values at each scheduled time point and change and percent change of CA-125 from baseline will be summarized descriptively.

CA-125 assessments will be presented in a by-subject listing.

4.2.3.3 Disease Control Rate

The DCR will be presented for the point estimate together with the exact Clopper-Pearson 95% CI.

4.2.3.4 Progression Free Survival

The number and percentage of subjects experiencing a PFS event and the type of event (progression or death), and subjects censored will be provided. The Kaplan-Meier estimate of the median PFS and the Brookmeyer-Crowley 95% CI will be presented. In addition, the proportion of subjects who are progression-free at clinically relevant time points (e.g. 6, 12, 18 and 24 months) will also be summarized.

Kaplan-Meier plots of PFS will be presented.

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.

4.2.3.5 Time to Earliest Progression by RECIST or CA-125, or Death

Summaries of the number and percentage of subjects experiencing a TTAP event and the type of event (progression per RECIST, CA-125 progression, CA-125 progression with RECIST progression, or death), and subjects censored will be provided. The Kaplan-Meier estimate of the median TTAP and the Brookmeyer-Crowley 95% CI will be presented. In addition, the proportion of subjects who are progression-free will be presented at clinically relevant time points (e.g. 6, 12, 18 and 24 months).

Kaplan-Meier plots of TTAP will be presented.

4.2.3.6 Overall Survival

Summaries of the number and percentage of subjects experiencing death and subjects censored will be provided. The Kaplan-Meier estimate of the median OS and Brookmeyer-Crowley 95% CI will be presented. In addition, the OS rate at clinically relevant time points (e.g. 6, 12, 18 and 24 months) will also be summarized.

Kaplan-Meier plots of OS will be presented.

4.2.4 Safety Analyses

Safety and tolerability will be assessed in terms of AEs (including SAEs, AESIs, and AEs leading to discontinuation), deaths, clinical laboratory evaluations, vital signs, ECGs, physical examinations findings, and ECOG performance status. Safety analyses will be based on the Safety Analysis Set.

Safety analyses in general will be descriptive and will be presented in tabular format with the appropriate summary statistics by cohort and overall.

4.2.4.1 Adverse Events

A TEAE is defined as an AE that emerges during the treatment period (from the first dose date of olaparib until 30 days after the last dosing date), having been absent at pre-treatment; or worsens in severity after treatment relative to the pre-treatment state. AESIs beginning after initiation of treatment will be included (i.e. treatment-emergent AESIs) in summaries.

An overview of AEs will be provided which summarizes subject incidence of the following:

- Any TEAEs
- Drug-related TEAEs
- NCI-CTCAE grade 3/4/5 TEAEs
- Drug-related NCI-CTCAE grade 3/4/5 TEAEs
- TEAE with an outcome of death
- Drug-related TEAE with an outcome of death
- Treatment-emergent SAEs
- Drug-related treatment-emergent SAEs
- Discontinuation due to TEAEs
- Discontinuation due to drug-related TEAEs

- AESIs
- Drug-related AESIs

The number and percentage of subjects with TEAEs will be tabulated by the maximum reported NCI-CTCAE grade, SOC and PT. Drug-related TEAEs, CTCAE grade 3/4/5 TEAEs, treatment-emergent SAEs, drug-related treatment-emergent SAEs, TEAEs leading to discontinuation of olaparib, and drug-related TEAEs leading to discontinuation of olaparib will be summarized in the same manner. For these summaries, subjects with multiple AEs will be counted only once by the maximum reported NCI-CTCAE grade within a given SOC and PT.

AESIs will be summarized by SOC and PT. Summaries will include the number and percentage of subjects who have:

- Any AESIs presented by outcome
- Drug-related AESIs
- Discontinuation due to AESIs

Additional summaries including the time to onset, prevalence over time, and duration of AEs in certain PTs or groups of PTs may be generated.

A by-subject listing of all AEs including verbatim term, PT, SOC, NCI-CTCAE grade, and relationship to study drug will be provided. Listings will also be provided of deaths, SAEs, AESIs, and AEs leading to discontinuation of olaparib.

4.2.4.2 Clinical Laboratory Evaluations

Descriptive statistics will be provided for selected clinical laboratory parameters (clinical chemistry, hematology, and urinalysis) including absolute measurements and changes from baseline by scheduled time of evaluation. Changes from baseline by scheduled time of evaluation will include end of treatment, 30 day follow-up, maximum post-treatment value, and minimum post-treatment value. Both scheduled and unscheduled post-treatment visits will be considered for the summaries of the maximum and minimum post-treatment values.

Abnormal laboratory results will be graded according to NCI-CTCAE version 4.03 as applicable. Shift tables, presenting the 2-way frequency tabulation for baseline and the worst post-treatment value (both decreased and increased separately) according to the NCI-CTCAE grade, will be provided for selected clinical laboratory tests. Both scheduled and unscheduled post-treatment visits will be considered in tabulation of the worst post-treatment value.

The number and percentage of subjects with the following potentially clinically significant abnormal liver function tests will be summarized:

- ALT $\geq$ 3 x ULN, $\geq$ 5 x ULN, $\geq$ 10 x ULN, and $\geq$ 20 x ULN

- AST ≥ 3 x ULN, ≥ 5 x ULN, ≥ 10 x ULN, and ≥ 20 x ULN
- ALT or AST ≥ 3 x ULN, ≥ 5 x ULN, ≥ 10 x ULN, and ≥ 20 x ULN
- Total bilirubin ≥ 2 x ULN
- ALP ≥ 1.5 x ULN and ≥ 3 x ULN
- Potential Hy's Law cases: ALT or AST ≥ 3xULN **together with** total bilirubin ≥ 2x ULN

All clinical laboratory data will be presented in by-subject listings.

4.2.4.3 Vital Signs

Descriptive statistics will be provided for vital signs measurements (systolic and diastolic blood pressure, pulse rate, body temperature, and weight) by scheduled time of evaluation.

All vital signs data will be presented in a by-subject listing.

4.2.4.4 ECGs

All ECG data will be presented in a by-subject listing.

4.2.4.5 ECOG Performance Status

A shift table presenting the 2-way frequency tabulation from the Screening period to the End-of-Study Treatment Visit (or last visit on-study) and worst post-baseline classification will be provided for ECOG performance status.

4.2.4.6 Physical Examination Findings

Physical examination findings will be presented in a by-subject listing. Both scheduled and unscheduled visits will be included.

4.2.4.7 Other Safety Analyses

All other safety variables (e.g. pregnancy test) will be presented in by-subject listings.

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[redacted]

[redacted]

5. INTERIM ANALYSES

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.

If a given cohort is terminated due to futility, certain analyses which require an objective radiological response (i.e. ORR and DoR) will not be calculated for that cohort only. Other analyses (e.g. safety analyses) will still be presented for a cohort terminating early for futility.

The stopping boundary for the interim futility analysis was determined from Binomial probabilities. With a true ORR of 5%, a cohort would terminate early for futility (no objective responses 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.

In addition, a descriptive analysis of ORR, secondary outcomes, and safety can be generated for abstract or presentation of the ongoing study at any time.

6. CHANGES OF ANALYSIS

In Study Protocol D0816L00003 (Version 3.0; 10 October 2017) the Efficacy Analysis Set comprises all subjects who received at least 1 dose of olaparib and had a baseline tumor assessment. For the purposes of analysis for efficacy endpoints this definition has been extended with the requirement of ‘measureable disease’. The Full Analysis Set has also been added (see Section 2.1).

7. REFERENCES

Brookmeyer, R. and Crowley, J. (1982). “A Confidence Interval for the Median Survival Time”. Biometrics. 38: 29–41.

Clopper, C. and Pearson, E. S. (1934). "The use of confidence or fiducial limits illustrated in the case of the binomial". Biometrika. 26: 404–413.