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AstraZeneca

Statistical Analysis Plan

Study Code	D0816C00016
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An Open Label, Single Arm, Multicentre Study to Assess the Clinical Efficacy and Safety of Lynparza (Olaparib) Tablets (150mg) Maintenance Monotherapy in Platinum Sensitive Relapsed Ovarian Cancer Patients who are in Complete or Partial Response Following Platinum based Chemotherapy (L-MOCA)

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Study Statistician PPD

19 February 2023 | 08:47 IST
Date

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Study Medical Advisor

PPD

2023年2月23日 | 07:56 CET
Date

PPD

2023年2月19日 | 04:37 AST
Date

PPD

2023年2月19日 | 22:42 AST
Date

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An Open Label, Single Arm, Multicentre Study to Assess the Clinical Efficacy and Safety of Lynparza (Olaparib) Tablets (150mg) Maintenance Monotherapy in Platinum Sensitive Relapsed Ovarian Cancer Patients who are in Complete or Partial Response Following Platinum based Chemotherapy (L-MOCA)

Global Product Statistician PPD

20 February 2023 | 12:06 CET
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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BRCA	Breast cancer susceptibility gene
BUN	Blood Urea Nitrogen
CI	Confidence Interval
CR	Complete Response
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Event
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group: a performance status using scales and criteria to assess how a patient's disease is progressing
FAS	Full Analysis Set
MedDRA	Medical Dictionary for Regulatory Activities
OAE	Other Significant Adverse Event
OS	Overall Survival
PFS	Progression Free Survival during initial olaparib maintenance therapy
PFS2	Progression Free Survival following initial olaparib maintenance and subsequent chemotherapy
PT	Preferred Term
RECIST	Response Evaluation Criteria in Solid tumours. This study will use RECIST version 1.1.
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOC	System Organ Class
TEAE	Treatment-emergent Adverse Event
TDT	Time to Discontinuation of Treatment
TFST	Time to First Subsequent Treatment

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Abbreviation or special term	Explanation
TSST	Time to Second Subsequent Treatment

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AMENDMENT HISTORY

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CATEGORY Change refers to:	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
N/A	5/24/2017	Initial approved SAP	N/A	N/A
Data presentation	11/15/2021	Add visit window and Imputation rule for missing dates handling	Yes, Version 3.0	
Statistical Analysis method for safety endpoints	11/15/2021	Add summary of all AEs besides of TEAEs	Yes, Version 3.0	Further replenish safety analysis
Exploratory Endpoints	11/15/2021	Amend Exploratory Endpoints according to Protocol Version 3.0	Yes, Version 3.0	Protocol amended for exploratory endpoints
Statistical Analysis method for exploratory endpoints	11/15/2021	Add description of statistical analysis method for exploratory endpoints as amended in	Yes, Version 3.0	Protocol amended for exploratory endpoints
Sample size	8/11/2022	Update sample size in Section 1.3	Yes, Version 3.0	To be consistent with CSP
Subgroup analyses	8/11/2022	Add subgroup analyses for exploratory	Yes, Version 3.0	Explore subgroup analysis
Exploratory Endpoints	8/11/2022	Add relationships analysis between PD-L1 expression and HRD/ BRCA/ HRR mutation status	Yes, Version 3.0	Explore biomarker relationships
Exploratory Endpoints	8/11/2022	Add biomarker interaction assessment with efficacy	Yes, Version 3.0	Explore biomarker interactions
Exploratory Endpoints	8/11/2022	Add sample test results consistency analysis	Yes, Version 3.0	Explore sample test consistency
Interim Analysis	2/1/2023	Add one interim analysis	Yes, Version 3.1	To be consistent with CSP
Exploratory Endpoints	2/1/2023	Add subgroup analyses of OS for exploratory	Yes, Version 3.1	Explore subgroup analysis

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Exploratory Endpoints	2/1/2023	Add PD-L1 CPS analysis	Yes, Version 3.1	Explore biomarker analysis

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1. STUDY DETAILS

1.1 Study objectives

1.1.1 Primary objective

Primary Objective:	Outcome Measure:
To assess the efficacy of olaparib maintenance monotherapy by investigator assessed progression free survival (PFS) according to RECIST 1.1 criteria.	Time from first dosing date of olaparib to date of disease progression or death from any cause (if this occurs before disease progression)

1.1.2 Secondary objectives

Secondary Objective:	Outcome Measure:
To assess the efficacy of olaparib maintenance monotherapy of BRCAm population by investigator assessed progression free survival (PFS) according to RECIST 1.1 criteria.	To assess the efficacy of olaparib maintenance monotherapy of BRCAm population by investigator assessed progression free survival (PFS) according to RECIST 1.1 criteria.
To assess the clinical efficacy of olaparib maintenance monotherapy by assessment of: a) overall survival (OS), b) time to investigator- assessed second progression (PFS2), or death, in patients with ovarian cancer.	a) Time from first dosing date of olaparib to date of death from any cause b) Time from first dosing date of olaparib to date of second progression event or death from any cause (if this occurs before second progression event)
To assess the clinical efficacy of olaparib maintenance monotherapy by assessment of a) time to first subsequent therapy or death (TFST), b) time to second subsequent therapy or death (TSST) and c) time to olaparib discontinuation or death (TDT) in patients with ovarian cancer.	a) Time from first dosing date of olaparib to date of first subsequent treatment commencement or death from any cause (if this occurs before commencement of first subsequent treatment) b) Time from first dosing date of olaparib to date of second subsequent treatment commencement or death from any cause (if this occurs before commencement of second subsequent treatment) c) Time from first dosing date of olaparib to date of olaparib discontinuation or death from any cause (if this occurs before discontinuation of olaparib maintenance therapy)

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1.1.3 Safety objectives

Safety Objective:	Outcome Measure:
To evaluate the safety and tolerability of olaparib.	AEs/SAEs Collection of clinical chemistry/haematology parameters

1.1.4 Exploratory objectives

Exploratory Objective:	Outcome Measure:
To explore biomarkers in tumor tissues or blood predictive of sensitivity/resistance to the treatment of olaparib	a) Immune-markers PD-L1 expression in tumor tissues b) *BRCA* and HRR mutation status in the cell-free DNA from blood samples c) HRD status in tumor samples d) Relation between having a HRD test and patient demographic and clinical characteristics

1.2 Study design

This is a prospective, open-label, single arm, multi-centre interventional study to assess the clinical efficacy and safety of olaparib maintenance monotherapy as the tablet formulation in PSR high grade (serous or endometrioid) epithelial ovarian cancer patients (including patients with primary peritoneal and/or fallopian tube cancer).

Patients will be assigned to olaparib tablets p.o. 300 mg twice daily. They should initiate olaparib treatment within 8 weeks after their last dose of chemotherapy (last dose is the day of the last infusion).

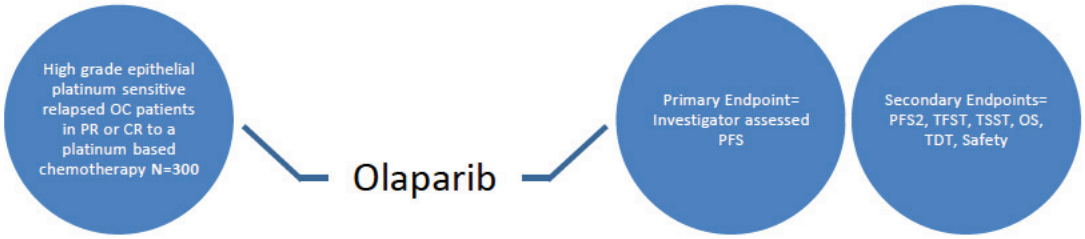
Patients must have clinical and objective radiological tumour assessments according to RECIST 1.1 criteria at baseline and every 12 weeks relative to date of enrolment, until objective radiological disease progression as determined by the investigator. Patients could continue to receive olaparib for as long as determined by the investigator, until objective radiological disease progression or as long as in the investigator's opinion they are benefiting from treatment in relation to other clinical assessments and they do not meet any other discontinuation criteria.

Once a patient has discontinued olaparib she will be managed as per local clinical practice but will remain in the study and data will be collected on subsequent treatments, progression and survival.

Study flow chat is shown in Figure 1.

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Figure 1 Study Flow Chart



Notes: OC ovarian cancer; PR partial response; CR complete response; PFS progression free survival; TFST time to first subsequent treatment; TSST time to second subsequent treatment; OS overall survival; TDT time to discontinuation of treatment;

1.3 Number of subjects

No formal sample size calculation is provided for this study. The sample size of approximately 220 patients is driven by the need to enrol an adequate number of patients to help understand the efficacy and safety of olaparib with the tablet formulation. Around 46 patients with BRCAm ovarian cancer will be enrolled assuming that BRCA mutation rate is 21%.

The primary analysis will be performed after the accumulation of 132 progression or death events which corresponds to 60% maturity. Assuming a median PFS value of 8.4 months, 132 PFS events will provide a 95% confidence interval of (7.1 m, 10.0 m) for the median PFS. Assuming a median PFS of 19.1 months in the BRCA mutated patients, 27 PFS events (60% of 46 BRCA mutated patients) will provide a 95% confidence interval of (13.1 m, 27.9 m) for the median PFS.

2. ANALYSIS SETS

2.1 Definition of analysis sets

Full analysis set (FAS)

The full analysis set will include all subjects who received at least one dose of study treatment.

All analyses will be performed based on the FAS.

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2.2 Violations and deviations

The Investigator(s) would document any deviation from the protocol regardless of their reasons. The important deviations will be listed and summarized. No deviation would be excluded from analysis according to the definition of FAS.

3. PRIMARY AND SECONDARY VARIABLES

3.1 General principles

3.1.1 Baseline definition

Unless otherwise stated, baseline will be defined as the last non-missing evaluation prior to first dosing (Day 1) of study treatment.

3.1.2 Study Day

If the assessment or event date is on or after the first dosing date of olaparib, the study day will be calculated as: Assessment Date – Date of First Dosing (Day 1) + 1.

If the assessment or event date is prior to the first dosing date of olaparib, the study day will be calculated as: Assessment Date – Date of First Dosing (Day 1).

3.1.3 Visit Windows

Time windows will need defining for any presentations that summarise values by visit. The following conventions should apply:

- The time windows should be exhaustive so that data recorded at any time point has the potential to be summarized. Inclusion within the time window should be based on the actual date and not the intended date of the visit.

- All unscheduled visit data should have the potential to be included in the summaries. For safety assessments, the window for the visits following baseline will be constructed in such a way that 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). If an even number of days exists between two consecutive visits then the upper limit will be taken as the midpoint value minus 1 day. i.e., the visit window for safety assessments of visit 2 will start from Day2.If several different assessments fall into a given visit window then the one closest to the protocol scheduled time point will be used. In two evaluations are equidistant from the scheduled time point, the earlier one will be used. While all values will be listed

- For tumour assessment, baseline assessments should be performed no more than 28 days before the start of study treatment, and ideally should be performed as close as possible to the start of study treatment. After baseline, follow-up very 12 weeks after start of treatment until objective disease progression as defined by RECIST 1.1, up to 72 weeks, then every 24 weeks relative to date of enrolment until progression.

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Analysis Visit	Target Day	Visit Window
Baseline	1	-28 ≤ Day ≤1
Visit 3	8	2 ≤ Day ≤11
Visit 4	15	12 ≤ Day ≤18
Visit 5	22	19 ≤ Day ≤25
Visit 6	29	26 ≤ Day ≤32
Visit 7	57	54 ≤ Day ≤60
Visits scheduled on the first day of every 4 weeks		
……		
Visit 34	813	804≤ Day ≤820
Visits scheduled on the first day of every 12 weeks		
Visit 35	897	890≤ Day ≤904
……		
End of Treatment		±7d
Follow-up Visit		±7d
Off Treatment Follow-up		
If IP treatment is discontinued due to other reasons rather than disease progression, then visits are scheduled every 12 weeks, otherwise perform tumour assessment visits every 12 or 24 weeks.		±7d
……		±7d
End of Study		±7d

3.1.4 Handling of missing data

As a general rule, missing data values will not be imputed in tumor assessments for efficacy analysis. The missing data handling rules for each statistical analysis are specified in relevant section.

3.2 Efficacy variables

3.2.1 Primary endpoint

The primary efficacy endpoint is progression free survival (PFS) as assessed by investigator according to RECIST 1.1 criteria.

PFS is defined as the time from first dose of olaparib until the date of investigator assessed disease progression according to RECIST 1.1 criteria or death from any cause (by any cause in the absence of disease progression) regardless of whether the patient withdraws from therapy or receives another anticancer therapy prior to disease progression. Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable efficacy assessment. However, if the patient progresses or dies after two or more missed visits, the patient will be censored at the time of the latest evaluable assessment. Given the scheduled visit assessment scheme, two missing visits will

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equate to more than 26 weeks since the previous RECIST assessment, allowing for early and late visits. If the patient has no evaluable visits or does not have a baseline assessment they will be censored at day 1 unless they die within two visits of baseline (25 weeks allowing for visit window).

The PFS time will always be derived based on scan/assessment dates 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 patient for PFS the patient 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.

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

3.2.2 Secondary endpoints

3.2.2.1 Overall Survival

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

If the date of death is missing, then the date will be imputed according the following rule:

- If the date is completely missing, there will be no imputation made, and patient will be censored at last known survival date;
- If month and day as missing, it will be imputed as January 1;
- If only the day is missing, it will be imputed as the 1st day of the month;

If the imputed date of death is prior to the last known survival date, then the date will be imputed as the last known survival date +1. If the imputed date of death is after the date of death that can be referenced (i.e. the date of the survival follow-up that gets the information of death), the date will be imputed as the referenced date-1. The last known survival date is the latest date of all dates, including lab, medication, tumor assessment, AE, etc.

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3.2.2.2 Time from first dose to second progression (PFS2)

Time to second progression is defined as the time from the date of first dose to the date of the earliest progression event subsequent to that used for the primary variable PFS or death from any cause. The date of second progression will be recorded by the investigator and defined according to local standard clinical practice and may involve any of objective radiological, symptomatic, CA-125 progression or death. Second progression status will be reviewed every 12 weeks following the progression event used for the primary variable PFS (the first progression) and status recorded. Patients alive and for whom a second disease progression has not been observed should be censored at the last time known to be alive and without a second disease progression, i.e. censored at the last assessment for progression date if the patient has not had a second progression or death.

3.2.2.3 Time to first subsequent treatment or death (TFST)

As a supportive summary to PFS, time to start of first subsequent treatment or death will be assessed. Time to first subsequent treatment or death is defined as the time from the date of first dose to the first subsequent treatment start date, or death date. Any patient not known to have had a further subsequent therapy or death will be censored at the last known time to have not received subsequent treatment.

If the date of first subsequent treatment is missing, then the date will be imputed according the following rule:

-
- If the date is completely missing, there will be no imputation made and patient will be censored at the last known time to have not received subsequent treatment; If month is missing, it will be imputed as January 1 or the last dose date +1, which comes later;
- If only the day is missing, it will be imputed as the 1st day of the month or the last dose date +1, which comes later;

3.2.2.4 Time to study treatment discontinuation or death (TDT)

Time to study treatment discontinuation or death (TDT) will be assessed. TDT is defined as the time from the date of first dose to the date of study treatment discontinuation or death from any cause. Any patient not known to have died at the time of analysis and not known to have discontinued study treatment will be censored based on the last recorded date on which the patient was known to be alive.

3.2.2.5 Time to second subsequent treatment or death (TSST)

As a supportive summary to PFS2, time to start of second subsequent treatment or death will be assessed. Time to second subsequent treatment or death is defined as the time from the date of

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first dose to the earlier of the date of second subsequent treatment start date, or death date. Any patient not known to have had a further second subsequent therapy or death will be censored at the last known time to have not received second subsequent treatment.

If the date of second subsequent treatment is missing, then the date will be imputed according the following rule:

- If the date is completely missing, there will be no imputation made and patient will be censored at the last known time to have not received second subsequent treatment;
- If month is missing, it will be imputed as January 1 or the first subsequent treatment date +1, which comes later;
- If only the day is missing, it will be imputed as the 1st day of the month or the first subsequent treatment date, which comes later;

3.3 Safety variables

Safety and tolerability endpoints include adverse events (AEs), laboratory tests (including clinical chemistry, haematology, urinalysis, Coagulation), vital signs, physical examination, Electrocardiogram (ECG), ECOG performance status and exposure.

3.3.1 Adverse events (AEs)

Adverse Events, including Serious Adverse Events, will be collected from time of signature of informed consent, throughout the treatment period and up to and including the 30-day follow-up period after last dose of study medication.

The endpoints of AEs include incidence of adverse events by worst CTC grade, treatment-related AEs, serious adverse events (SAEs), Death, AEs leading to discontinuation of study therapy and other significant adverse events (OAEs).

Adverse events will be coded by Medical Dictionary for Regulatory Activities (MedDRA 19.1 or higher) and graded according to National Cancer Institute(NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

3.3.1.1 Other significant adverse events (OAE)

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and discontinuation of investigational product due to adverse events (DAEs). Based on the expert's judgement, significant adverse events of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered OAEs and reported as such in the Clinical Study Report. A similar review of laboratory/vital signs will be performed for identification of OAEs. Examples of these are marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment.

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3.3.2 Laboratory Data

The laboratory data includes clinical chemistry, haematology, urinalysis, coagulation (Activated partial thromboblastin time (APTT), International normalised ratio (INR)). The detailed list of clinical chemistry, haematology and urinalysis parameters is listed in Table 1.

Table 1 Laboratory Safety Variables

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

3.3.3 Vital Signs

Vital signs include height, weight, blood pressure, pulse and body temperature. Change from baseline in blood pressure, pulse, temperature and weight will be calculated where the baseline value will be the latest result obtained prior to the start of investigational product.

3.3.4 Physical Examination

Physical examination will be performed at screening, baseline and as clinically indicated.

3.3.5 ECGs

Twelve-lead ECGs will be obtained within 7 days prior to starting study treatment and when clinically indicated. All ECGs should be assessed by the investigator as to whether they are clinically significantly abnormal / not clinically significantly abnormal.

3.3.6 ECOG Performance Status

Performance status will be obtained at screening, subsequent on treatment visit and treatment discontinued visit and will be assessed according to ECOG criteria as follows:

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Grade	Description
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 housework or office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about > 50% of waking hours
3	Capable of only limited self-care, confined to a bed or chair > 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

3.3.7 Exposure

Duration of exposure to investigational product will be defined in months as:

Total treatment exposure (months) = [(last dose date where dose > 0mg - first dose date where dose > 0mg) +1] / (365.25/12).

Actual treatment exposure excludes the duration of dose interruptions from the total treatment duration. The formula for it is below:

Actual treatment exposure = (last dose date where dose > 0 mg – first dose date where dose > 0 mg + 1 – total duration of dose interruption (i.e. number of days with dose = 0 mg))/ (365.25/12).

Note the actual exposure calculation makes no adjustment for any dose reductions that may have occurred.

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4. ANALYSIS METHODS

Data will be analyzed on the FAS population. The primary analysis will be performed at the time of accrual of 180 progression or death events in the 300 enrolled patients. The final analysis will be performed when approximately 60% OS maturity is achieved.

4.1 General principles

All data recorded on case report form (CRF) will be listed by subject. Continuous variables will be summarized using descriptive statistics (i.e. n, mean, standard deviation (SD), median, quartiles (Q1 and Q3), minimum, and maximum). Categorical variables will be summarized using the frequency counts and percentages for each category. The median value and 95% CI of the time-dependent variables (e.g. PFS, PFS2, TFST, TSST, TDT) will be estimated with Kaplan-Meier method.

For the summary statistics of all numerical variables unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported. Mean and median will be displayed to one level of precision greater than the data collected. Standard deviation/standard error will be displayed to two levels of precision greater than the data collected.

The default significant level will be (5%); confidence intervals (CIs) will be 95% and all tests will be two-sided, unless otherwise specified in the description of the analyses.

P-values will be rounded to three decimal places. If a p-value is less than 0.001 it will be reported as “<0.001.” If a p-value is greater than 0.999 it will be reported as “>0.999.”

SAS® version 9.2 or higher will be used for statistical analyses, tabulations and graphical presentations.

4.2 Analysis Methods

4.2.1 Subject Information

4.2.1.1 Disposition of Subjects

Patients disposition will be listed and summarized the number of patients: screened, enrolled, treated in full analysis set.

In addition, the number and percentage of patients who failed screening will be summarized, and also the number and percentage of patients who discontinued treatment and who discontinued the study and reasons for discontinuation will be summarized.

4.2.1.2 Protocol Deviations

All the important protocol deviations will be listed and summarized for the FAS.

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4.2.1.3 Demographics and Baseline Characteristics

Demographic and baseline patient characteristics will be listed and summarized for the FAS.

Continuous demographic and baseline variables include age (years), baseline weight (kg), height (cm), baseline Body mass index (BMI) (kg/m^2) and baseline tumor size which OAEwill be summarized using descriptive statistics.

The total counts and percentages of patients will be presented for the categorical variables of age (<65years vs. ≥65years), race, ethnicity, Disease Stage at Primary Diagnosis, primary tumor location, histology type, known sites of locally advanced and metastatic disease.

4.2.1.4 Medical History

The Medical History will be coded by MedDRA (version 19.1 or higher). The number and percentage of patients with any medical history will be summarized for the FAS by system organ class (SOC) and preferred term (PT). All disease related medical history will be listed.

4.2.1.5 Prior and Concomitant Therapy

Prior and concomitant medications

All investigator terms for medications recorded on the CRF will be coded using the World Health Organization (WHO) Drug Dictionary (WHO2015Q1 version or higher). The number and percentage of patients who take at least one prior and concomitant medications will be summarized on the FAS by Anatomical Therapeutic Chemical (ATC) Classification and WHO Drug PT. All prior and concomitant medication data will be presented in listings.

Prior medications are defined as those medications with an end date prior to first dose of olaparib. Concomitant medications are defined as those medications which are taken on or after the first dose of olaparib (Day 1). This includes medications which start prior to Day 1 but continue while the subject is on treatment.

STOP Dates Imputation rules: For medications with partial stop dates, if start date of medication is on or after treatment start date of IP then concomitant. Else please refer to follow table to distinguish prior/concomitant medications:

Table 2 Handling of partial STOP date

Known part	Missing part	Prior or Concomitant
None	Year, Month, Day	Concomitant
Month, Day	Year	Concomitant
Year	Month, Day	Prior if year < year of first administrated date of IP, otherwise Concomitant

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Year, Month	Day	Prior if year and month < year and month of first administrated date of IP, otherwise Concomitant
Year, Day	Month	Prior if year < year of first administrated date of IP, otherwise Concomitant

The concomitant procedure will be coded by MedDRA (version 19.1 or higher). The number and percentage of patients with any concomitant procedure will be summarized for the FAS by system organ class (SOC) and preferred term (PT).

Prior Surgeries

The surgical history will be coded by MedDRA (version 19.1 or higher). The number and percentage of patients with any surgical history will be summarized for the FAS by system organ class (SOC) and preferred term (PT). All surgical history will be listed.

Prior anti-cancer therapies

The number and percentage of patients with any prior anti-cancer therapies including by therapy class, best response, treatment status and classification of platinum sensitivity will be summarized in the FAS. The chemotherapy will be coded using the WHO Drug Dictionary (WHO2015Q1 version or higher) and summarized by ATC Classification and WHO Drug PT. Any prior anti-cancer therapies will be listed.

The number and percentage of patients with any prior radiotherapies，radiotherapies' total dose, fraction dose and treatment status will be summarized in the FAS. Any radiotherapies will be listed.

Imputation method of missing prior cancer therapy date:

1) If only the day is missing, the date will be set to the first day of the month,
2) If year or month is missing, then it will be kept missing.

Subsequent therapies for cancer

The number and percentage of patients with any subsequent therapies for cancer and/or surgery for the treatment of the cancer, after discontinuation of treatment, will be summarized in the FAS. Reasons for starting subsequent anti-cancer therapies will also be summarized.

Subsequent therapies for cancer and/or surgery for the treatment of the cancer, after discontinuation of treatment will be listed.

Imputation method of missing date of subsequent cancer therapy:

1) If only the day is missing, the date will be set to the first day of the month,
2) If year or month is missing, then it will be kept missing.

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4.2.1.6 Treatment Compliance

Descriptive summary statistics will be provided for compliance in the FAS. Mean, standard deviation, median, minimum, and maximum of compliance will be provided. The cell frequencies and percentage of patients in each category (<80%, >=80% and <=120%, >120%) will be provided.

The compliance (%) is calculated as: (the amount of drug used / the amount of drug planned) ×100, where:

- The amount of drug used = the amount of drug dispensed – (the amount of drug returned + the amount of drug lost).
- The amount of drug planned = the planned dosage daily × planned treatment days.
- Planned treatment days = last planed dose date – first dose date + 1, excluding dose interruptions.

4.3 Efficacy Analyses

4.3.1 Analysis of the primary variable (s)

PFS will be analysed when approximately 132 progression events have occurred in the study (60% maturity). This analysis will address the primary objective of the trial. The updated results will also be provided at the final analysis.

A Kaplan-Meier (KM) plot of PFS will be presented. Summaries of the number and percentage of patients experiencing a PFS event, and the type of event (progression or death) will be provided along with median PFS and 95% confidence interval.

The analysis on PFS will be based on RECIST 1.1 criteria assessed by investigators, 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 summarised (using the KM curve) for all patients.

The number of patients prematurely censored will be summarised together with baseline prognostic factors of the prematurely censored patients. A patient is defined as prematurely censored if they had not progressed and the latest scan prior to the date of cut off (DCO) was more than one scheduled tumour assessment interval (+ 2 weeks) prior to the DCO date.

4.3.2 Analysis of the secondary variable(s)

All time to event endpoints will be described as for PFS. The minimum and maximum follow-up time will be reported and the median follow-up duration will be calculated.

4.3.3 Subgroup analysis

Subgroup analyses will be performed, as described for the primary analysis of PFS and secondary analysis of OS, to assess the consistency of olaparib effect across potential or expected prognostic factors.

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The following subgroups of the PFS may be summarised when applicable (i.e., with at least 5 observations).

- Response to last previous platinum based chemotherapy (CR vs PR)
- Time to disease progression on second to last platinum based chemotherapy received prior to first dose of olaparib (6 – 12 months / > 12 months)
- Measurable versus non-measurable disease at baseline
- *BRCA* mutation type, e.g. (BRCA1, BRCA2, BRCA1/2, and further specified by germline or somatic mutation)
- *HRR* mutation type
- *HRD mutation*
- Age at first dose (<65 vs. ≥65)
- Country
- Prior bevacizumab use
- Prior chemotherapy lines (Second line, Third line, Fourth line and beyond)

Other baseline variables may also be assessed if there is clinical justification.

4.4 Safety analyses

Safety data will be analyzed on the FAS population.

For change from baseline summaries for vital signs, laboratory data, ECGs, ECOG Performance Status and physical examination, the baseline value will be the latest result obtained prior to the start of investigational product.

4.4.1 Extent of Exposure

The treatment exposure (total and actual which excludes dose interruptions) will be summarized using descriptive statistics. The number and percentage of patients with dose reductions and interruptions will be presented and the durations will be summarized. The main reason for dose modification/interruption will be listed, and summarized if appropriate. All dosing data will be listed.

4.4.2 Adverse Events

Adverse events will be coded to primary System Organ Class (SOC) and preferred term (PT) using MedDRA (version 19.1 or higher).

A treatment-emergent adverse event (TEAE) is defined as an AE that had an onset date, or a worsening in severity from baseline (pre-treatment), on or after the first dose of study drug up to 30 days of discontinuation of investigational product following study drug discontinuation. All AEs (TEAE or AEs occurring before treatment with study drug, or AEs occurring more than 30 days after discontinuation of study drug) will be listed. Deaths, SAEs and Other Significant Adverse Events will also be presented in separate subject data listings.

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Start Date Imputation Rule: For AEs with partial onset date, if end date of AE occurring is prior to treatment start date of IP then not TEAE. Else please refer to follow table when start date of AE is incomplete:

Table 3 Handling of partial START date

Known part	Missing part	Is TEAE?
None	Year, Month, Day	Yes
Month, Day	Year	Yes
Year	Month, Day	Not TEAE if year < year of first administrated date of IP, otherwise TEAE
Year, Month	Day	Not TEAE if year and month < year and month of first administrated date of IP, otherwise TEAE
Year, Day	Month	Not TEAE if year < year of first administrated date of IP, otherwise TEAE

An overview table will summarize the number and percentage of patients with at least one of the following AEs even if the subject experienced more than one TEAE in a particular category.

- Any TEAE.
- Any treatment-related TEAE.
- Any TEAE of CTCAE grade 3 or higher.
- Any TEAE of CTCAE grade 3 or higher, casually related to study drug.
- Any TEAE resulting in death.
- Any TEAE leading to discontinuation of study drug.
- Any TEAE leading to dose modification.
- Any treatment-emergent SAE.
- Any treatment-emergent SAE, causally related to study drug.
- Any treatment-emergent SAE leading to discontinuation of study drug.

The incidence of TEAEs will be reported as the number and percentage of subjects with TEAEs within SOC and PT. Subjects will be counted only once within a SOC and PT, even if the subject experienced more than one TEAE within a specific SOC and PT. The number and percentage of subjects with TEAEs will also be summarized by maximum CTC grade where multiple AEs within a particular SOC or PT will be counted under the category of their most severe AE within that SOC or PT. The following summaries will be produced:

- TEAEs by SOC and PT.
- TEAEs by maximum reported CTCAE grade, by SOC and PT.
- TEAEs by severity and by SOC and PT.
- TEAEs of CTCAE grade 3 or higher, by SOC and PT.
- TEAEs causally related to study drug, by SOC and PT.
- TEAEs with outcome of death, by SOC and PT.

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- TEAEs with outcome of death, causally related to study drug, by SOC and PT.
- Treatment-emergent SAEs by SOC and PT.
- Treatment-emergent SAEs causally related to study drug, by SOC and PT.
- TEAE leading to discontinuation of study drug, by SOC and PT.
- TEAE leading to dose modification, by SOC and PT.
- Treatment-emergent OAEs by SOC and PT.In addition to TEAE, all AEs collected will be summarized in the same way as displayed above.

4.4.3 Clinical Laboratory Parameters

Laboratory results will be summarized using Système International (SI) units. All laboratory data recorded on CRF will be listed.

For all quantitative parameters, such as variables of haematology and clinical chemistry (listed in Section 3.3.2 of the SAP), the actual value and the change from baseline to each post-baseline visit will be summarized by visit using descriptive statistics. Corresponding shift tables from baseline to maximum toxicity CTCAE grade during treatment will be presented.

For qualitative parameters, such as variables of urinalysis will be summarized using frequencies (number and percentage of subjects) at each visit. Percentages will be based on the number of subjects with assessment at that visit. Corresponding shift tables will be produced from baseline to highest post-baseline value on treatment for urinalysis.

The laboratory parameters will also be summarized using the categories of normal, abnormal with no clinical significance (NCS) and abnormal with clinical significance (CS).

Hy's law

The number and percentage of subjects with the following laboratory abnormalities elevations in liver biochemistry will be summarized:

- ALT > 3 x ULN
- AST > 3 x ULN
- TBL > 2 x ULN
- ALT or AST > 3 x ULN and TBL> 2 x ULN.

4.4.4 Vital Signs, Physical Examination Findings, and ECGs

4.4.4.1 Vital Signs

Descriptive statistics for vital signs parameters (diastolic and systolic blood pressure, pulse rate, temperature, height, weight, and BMI) will be presented. All vital signs data will be listed.

4.4.4.2 Physical Examinations

For each physical examination body system, the number and percentage of patients with abnormalities at baseline will be summarized. All physical examination abnormal findings will be listed.

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4.4.4.3 ECGs

Descriptive statistics for ECG parameters will be presented per visit. Each variable will also be summarized using frequencies (number and percentage) by the classification of normal, abnormal with NCS and abnormal with CS per visit.

All ECG data will be listed.

4.4.4.4 ECOG Performance Status

The number and percentage of subjects will be presented by ECOG criteria (0, 1, 2, 3, 4, and 5) per visit. In addition, ECOG performance status will be compared with baseline levels with descriptive statistics using a shift table.

4.4.4.5 Pregnancy Test

The number and percentage of subjects will be presented by pregnancy test results per visit. While all pregnancy testing data will be listed.

4.5 Exploratory analysis

4.5.1 Immune-markers PD-L1 expression in tumour tissues

Distribution of patients falling into different range of PD-L1 expression (percentage of positive in tumour cell and immune cell, combined positive score) will be summarized. Results will be present in form of percentage and by type of cell. Actual cut-off values for different groups of ranges will be set per consultation from translational scientists.

To explore relationships between PD-L1 expression status and BRCA and HRR mutation status, PD-L1 expression status with consultative cut-offs will be summarized by subgroups, including patients with different tissue HRR mutation status (mutation/ wild type), different ctDNA HRR mutation status (mutation/ wild type), as well as different tissue BRCA1/2 mutation status (mutation/ wild type).

4.5.2 BRCA and HRR mutation status in the cell-free DNA from blood samples

BRCA and HRR mutation status as tested in cell-free DNA from blood sample will be summarized per same method as for tumour sample. Where the results will be presented in form of count and percentage, and missingness will be presented as a separate category.

Subgroup analysis of PFS by BRCA and HRR mutation status as from blood sample will also be conducted per same method as for tumour sample. When applicable, a summary table might be provided to present the testing results with different samples (tissue BRCA and ctDNA BRCA, tissue HRR and ctDNA HRR). Meanwhile, a further subgroup analysis of PFS by both BRCA mutation (BRCA1/2 or BRCA wildtype) and Treatment Status of Study treatment (Second-Line or Third Line and beyond) might also be conducted when applicable (i.e., with at least 5 observations).

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4.5.3 HRD status in tumour samples

HRD testing results will be summarized in form of count and percentage of patients with positive or negative, where percentage will be based on number of FAS patients unless otherwise specified

Besides, the testing results of other biomarkers (BRCA and HRR) will also be summarized by the subgroup of patients with different HRD testing result. Analysis method will be same as for HRD and percentage will be based on patients with HRD testing result of positive/negative. When applicable (enough patients with available testing results and the assumption for correlation testing could be met).

Also, subgroup analysis of PFS will be conducted with patients of different HRD testing results if applicable.

A summary table will be displayed for patients with effective HRD status (positive/negative) , knowing consistency of between HRD status and HRR gene mutation results from tissue /blood sample.

4.5.4 Relation between having a HRD test and patient demographic and clinical characteristics

Due to the retrospective nature of the study, and that tissue testing for BRCA status will be carried out first, HRD testing will only be possible in those patients with remaining tumour sample/FFPE sample of sufficient quality and quantity. To ascertain whether systematic differences exist between patients with and without necessary tumour sample (or in effect a HRD test), the relation between having a HRD test and patient demographic and clinical characteristics will be investigated.

Subgroup analysis of patients having or not having HRD test will be conducted where patients demographic and clinical characteristics will be summarised. Regarding variables might include but not limited to: Age (<65years vs. ≥65years), Country, Stage at Primary Diagnosis , Response to Last Previous Platinum Based Chemotherapy (CR/PR), Time to Disease Progression on Second to Last Prior Platinum Based Chemotherapy (6-12 months/>12 month), Disease at baseline (Measurable/Not measurable), Prior Bevacizumab (Yes/No)..

4.5.5 Assess the role of biomarker interactions in PFS

Whole blood sample and tumour sample is collected as part of the study screening procedures and will be analysed for exploratory biomarkers interaction to assess correlations with PFS.

Subgroup analysis of PFS by both PD-L1 expression status in immune cell with consultative cut-offs and tissue HRR mutation status (mutation/ wild type) should also be conducted when applicable (i.e., with at least 5 observations). Kaplan-Meier (KM) plot of PFS will be presented.

The same subgroup analysis should be applied to all the following biomarker combinations:

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- PD-L1 expression status in immune cell and tissue HRR mutation status
- PD-L1 expression status in immune cell and ctDNA HRR mutation status
- PD-L1 expression status in immune cell and tissue BRCA1/2 mutation status
- PD-L1 expression status in immune cell and ctDNA BRCA1/2 mutation status
- PD-L1 expression status in immune cell and tissue HRD status
- PD-L1 expression status in tumour cell and tissue HRR mutation status
- PD-L1 expression status in tumour cell and ctDNA HRR mutation status
- PD-L1 expression status in tumour cell and tissue BRCA1/2 mutation status
- PD-L1 expression status in tumour cell and ctDNA BRCA1/2 mutation status
- PD-L1 expression status in tumour cell and tissue HRD status
- PD-L1 expression status in combined positive score and tissue HRR mutation status
- PD-L1 expression status in combined positive score and ctDNA HRR mutation status
- PD-L1 expression status in combined positive score and tissue BRCA1/2 mutation status
- PD-L1 expression status in combined positive score and ctDNA BRCA1/2 mutation status
- PD-L1 expression status in combined positive score and tissue HRD status

4.5.6 Assess the relationship between BRCA mutation status and Prior chemotherapy lines with PFS and OS

Exploratory subgroup analysis of PFS and OS by both BRCA mutation status (mutation/ wild type) in tumour cell and prior chemotherapy lines (second line/ third line and above) should be conducted when applicable (i.e., with at least 5 observations). Kaplan-Meier (KM) plot will also be presented.

The analysis should be applied to all the following subgroups:

- BRCA mutation in tumour cell
- BRCA wild type in tumour cell
- Second line in prior chemotherapy lines
- Third line and above in prior chemotherapy lines
- BRCA mutation in tumour cell and Second line in prior chemotherapy lines
- BRCA mutation in tumour cell and Third line and above in prior chemotherapy lines
- BRCA wild type in tumour cell and Second line in prior chemotherapy lines
- BRCA wild type in tumour cell and Third line and above in prior chemotherapy lines

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5. INTERIM ANALYSES

Interim analysis are planned 3 years after last patients enrolled if 60% OS maturity is not achieved by then. All Efficacy and Safety TFLs will be generated. But if the OS is not mature, median OS will not be published.

6. CHANGES OF ANALYSIS FROM PROTOCOL

This SAP is drafted based on Protocol V2.0. Currently no change of analysis is made from protocol.

7. REFERENCES

Collett 1994

Collett D. Modelling survival data in medical research Chapman & Hall/CRC 1994.

Eisenhauer et al 2009

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-247.

8. APPENDIX

Table 4 Study Schedule Screening

Day	**-28 to –1 (First visit)**
Informed consent	X
Demographics	X
Medical and surgical history	X
Prior cancer therapies including radiotherapy, response to current chemotherapy regimen	X
History of blood transfusions[a]	X
Inclusion/exclusion criteria	X
ECOG Performance Status (0-1)	X
Physical examination	X
Vital signs, body weight, (includes blood pressure [BP] and pulse)	X
ECG[b]	X

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Haematology / clinical chemistry[c]	X
Urinalysis	X
Pregnancy test[d]	X
Tumour Assessment (CT or MRI according to RECIST 1.1 criteria)[e]	X
Blood sample for disease specific marker (CA-125)	X
Blood sample for determination of *gBRCA* and other non *BRCA* germline HRR status[f]	X
Tumour sample for determination of *sBRCA* and other non-*BRCA* HRR gene mutation status[g]	X
Adverse Events (from time of consent)[h]	X
Relevant concomitant medications	X

[a] Include history of blood transfusion within previous 120 days from start of study treatment and the reasons e.g. bleeding or myelosuppression.

[b] ECG should be performed once the patient has been in the supine position for at least 5 minutes.

[c] Coagulation test should be performed at screening and if clinically indicated. For a list of all required laboratory tests please refer to Section 5.2.1**Error! Reference source not found.**.

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

[e] RECIST assessments will be performed using CT or MRI scans of neck, chest, abdomen, pelvis. Any other areas of disease involvement should be additionally imaged based on the signs and symptoms of individual patients. Baseline assessments should be performed no more than 28 days before the start of study treatment, and ideally should be performed as close as possible to the start of study treatment.

[f] The remaining samples will be used for exploratory analysis: BRCA and HRR mutation status in the cell-free DNA

[g] The remaining samples will be used for exploratory analysis:Immune-markers PD-L1

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

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Table 5 Study Schedule – On Study Treatment and Discontinuation

Visit Number	**2**	**3**	**4**	**5**	**6**	**Visit No. 7 onwards** Subsequent on treatment visits every 4 or 12 weeks[a] Tumour assessment visits every 12 or 24 weeks[a,f]	**Study treatment discontinued**	**Follow-up 30 days after last dose of IP**
Day	1	8	15	22	29	Day 1of next visit period (Visit 7 equals day 57 then visit 8 equals day 85 etc)		
Visit Window		*±3d*	*±3d*	*±3d*	*±3d*	*±3d*	*±7d*	*±7d*
Enrolment	X							
Physical exam[c]	X[b]							
Vital signs, body weight (includes BP, pulse and temperature) [c]	X[b]							
ECOG performance status	X					X	X	
ECG[c]	X[b]							
Haematology / clinical chemistry[d,k]	X[b]	X	X	X	X	X	X	X
Urinalysis[c]	X[b]							
Pregnancy test [e]	X				X	X		
Blood sample for disease specific marker (CA-125) [k]	X				X	X	X	

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Tumour Assessment (CT or MRI according to modified RECIST 1.1)[f]						X[f] [Every 12 weeks (±7d) [f]]		
Adverse Events [g,k]	X	X	X	X	X	X	X	X
Concomitant medications including blood transfusions	X	X	X	X	X	X	X	X
Olaparib dispensed/ returned [h,k]	X				X[h]	X[h]	X	
Subsequent cancer therapy following discontinuation of study treatment [i]								X
Time to second progression [j,k]						X		
Survival [k]						X		

[a] Visit to take place on Day 1 of a 4 week (28 day) visit period up to 120 weeks (if not progressed and still on treatment, or on study treatment post progression), then on day 1 of a 12 week visit period relative to date of enrolment.

[b] If assessed within 7 days before enrolment and meets the stated eligibility criteria (if applicable), it does not need to be repeated on Day 1 of study treatment unless investigator believes that it is likely to have changed significantly.

[c] To be additionally performed if clinically indicated at any other time.

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

[e] 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 2 during study treatment and at the 30 day follow up visit If results are positive the patient is ineligible/must be discontinued from study treatment immediately.

[f] Follow-up very 12 weeks after start of treatment until objective disease progression as defined by RECIST 1.1, up to 72 weeks, then every 24 weeks relative to date of enrolment. Any other sites at which new disease is suspected should also be appropriately imaged. If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits.

[g] When an AE for nausea and vomiting occurs, an additional eCRF will require completion. All ongoing adverse events/serious adverse events

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(AEs/SAEs) and any new AEs/SAEs identified during the 30 calendar days follow up period after last dose of study medication must be followed to resolution.

h Sufficient study treatment should be dispensed for at least each treatment period plus overage.

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

j Only patients on treatment post progression are required to undergo this procedure.

K Patients on treatment post progression are only required to undergo these procedures.

Table 6 Study Schedule –Follow up Post Discontinuation of Study Treatment

Visit Number	**Off treatment follow up** **Study treatment discontinued due to reasons other than disease progression** **Visits every 12 weeks Follow up for 1st progression Tumour assessment visits every 12 weeks or 24 weeks[a]**	**Time to second progression (PFS2) and Survival for:** • Patients who have discontinued study treatment due to disease progression • Patients who have progressed off treatment • Patients who were on study treatment post progression and / or after primary (PFS) analysis who subsequently discontinued study treatment **Every 12 weeks post discontinuation of study treatment**
Visit Window	±7d	±7d
Blood sample for disease specific marker (CA-125)	X	
Tumour Assessment (CT or MRI according to modified RECIST v1.1)[a]	X	
Adverse Events[b]	X	X

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Table 6 Study Schedule –Follow up Post Discontinuation of Study Treatment

Visit Number	Off treatment follow up Study treatment discontinued due to reasons other than disease progression Visits every 12 weeks Follow up for 1st progression Tumour assessment visits every 12 weeks or 24 weeks[a]	Time to second progression (PFS2) and Survival for: • Patients who have discontinued study treatment due to disease progression • Patients who have progressed off treatment • Patients who were on study treatment post progression and / or after primary (PFS) analysis who subsequently discontinued study treatment Every 12 weeks post discontinuation of study treatment
ECOG performance status	X	X
Subsequent cancer therapy following discontinuation of study treatment [c]	X	X
Time to second progression		X
Survival [de]	X	X

[a] RECIST follow-up assessments will be performed every 12 weeks (±1 week), up to 72 weeks, then every 24 weeks (±1 week) relative to date of enrolment. Follow-up assessment will include CT or MRI assessments of abdomen and pelvis for all patients. Follow-up chest CT will be performed (in those patients with thoracic lesions or upper abdomen lymphadenopathy identified at baseline assessment). Any other sites at which new disease is suspected should also be appropriately imaged. Patients must be followed until RECIST disease progression. If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits. Following disease progression further RECIST assessments will not be performed and assessment of disease will be as per local clinical practice.

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

[c] All anti-cancer treatments (including, but not limited to, chemotherapy and targeted agents), and the Investigators opinion of response to them and the date of progression need to be recorded.

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

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[e] In addition to their regular 12 weekly contact, patients will be contacted in the 7 days following a specified date (data cut off date) for each survival analysis.