Statistical Analysis Plan: I4D-MC-JTJN (V1)

A Phase 2 Study of Prexasertib in Platinum-Resistant or Refractory Recurrent Ovarian Cancer

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1. Statistical Analysis Plan: I4D-MC-JTJN: A Phase 2 Study of Prexasertib in Platinum-Resistant or Refractory Recurrent Ovarian Cancer

Confidential Information

Prexasertib (LY2606368) Ovarian Cancer

This study is a multicenter, nonrandomized, parallel cohort, Phase 2 study in patients with high-grade serous ovarian, primary peritoneal, or fallopian tube cancer. Patients will be assigned to cohorts based on their *BRCA* status and response to the platinum-based chemotherapy.

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Protocol I4D-MC-JTJN
Phase 2

Statistical Analysis Plan Version 1 electronically signed and approved by Lilly on date provided below.

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Revision History

SAP Version 1 was approved prior to the first patient visit.

3. Study Objectives

Table JTJN.4.1 shows the objectives and endpoints of the study.

Table JTJN.4.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
To estimate the ORR for each cohort	• ORR: proportion of all enrolled patients who achieve a best overall response of PR+CR as determined per RECIST version 1.1.
Secondary	
To characterize the safety and toxicity profile of prexasertib	• The safety endpoints evaluated will include but are not limited to the following: AEs, SAEs, clinical laboratory tests, ECGs vital signs, and physical examinations
To characterize the PK of prexasertib	• Prexasertib concentrations in plasma
To estimate secondary efficacy measures including DCR, DoR, CA-125 response, PFS, OS	• DCR: proportion of patients who achieve a best overall response of CR, PR and SD (for at least 4 months) as determined per RECIST version 1.1. • DoR: time from the date measurement criteria for CR or PR (whichever is first recorded) are first met until the first date of documented PD, per RECIST 1.1 criteria, or the date of death from any cause in the absence of documented PD. • CA-125 response: at least a 50% reduction in CA-125 levels from a pretreatment sample that is at least twice the upper limit of the reference range and obtained within 2 weeks before starting the treatment, with confirmation after 4 weeks according to GCIG criteria. • PFS: time from enrollment until the first radiographic documentation (as assessed by the investigator) of progression or death from any cause in the absence of documented PD • OS: time from enrollment until death from any cause
Tertiary/Exploratory	
To assess the relationship between biomarkers, prexasertib exposure (PK), and clinical outcomes	• Biomarker research assessed from blood or tissue samples, unless precluded by local regulations • Plasma concentration of prexasertib • Clinical outcomes data
To evaluate the patient-reported outcomes using NCCN-FACT-FOSI 18 and Worst Pain NRS	• Change from baseline • Time to progression • Association between time to pain progression and analgesic consumption • Association between time to progression and select efficacy outcomes

Abbreviations: AEs = adverse events; CR = complete response; DCR = disease control rate; DoR = duration of response; ECG = electrocardiogram; GCIG =Gynecologic Cancer InterGroup; NFOSI-18 = National Comprehensive Cancer Network – Functional Assessment of Cancer Therapy – Ovarian Symptom Index-18; NRS = numeric rating scale; ORR = overall response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PK = pharmacokinetics; PR = partial response; RECIST = Response Evaluation Criteria In Solid Tumors version 1.1 (Eisenhauer et al. 2009); SAEs = serious adverse events; SD = stable disease.

4. Study Design

4.1. Summary of Study Design

Study I4D-MC-JTJN is a multicenter, nonrandomized, parallel cohort, Phase 2 study in approximately up to 180 patients with high-grade serous ovarian, primary peritoneal, or fallopian tube cancer. Patients will be assigned to the following cohorts:

- Cohort 1: Platinum-resistant, *BRCA* negative, and received ≥3 lines of prior therapy
- Cohort 2: Platinum-resistant, *BRCA* negative, and received <3 lines of prior therapy
- Cohort 3: Platinum-resistant, *BRCA* positive, there is no restriction on number of lines of prior therapy, but must have received prior PARP inhibitor
- Cohort 4: Platinum-refractory, *BRCA* positive or negative, no restrictions on number of lines of prior therapy

The study employs a Bayesian adaptive design that may close enrollment in specific cohorts early based on the interim analysis results during the course of the trial. The study will initially enroll approximately 20 patients to each cohort and then a Bayesian model will be used to evaluate the posterior probability of activity for each cohort. A cohort will be closed if the posterior probability of activity is <20%. Subsequent interim analyses will be done to further evaluate the posterior probability of activity after additional patients are enrolled to each cohort.

4.2. Determination of Sample Size

The maximum total sample size of this study is estimated to be approximately 180 patients. For each of the 4 cohorts, the minimum sample size is approximately 20 patients. The sample size for each cohort will be dependent on the outcomes of the interim analyses. As cohorts are halted, new eligible patients will be allocated to the enrolling cohorts. As a result, the maximum sample size of a single cohort is approximately 120 patients (e.g., if enrollment to all but one of the cohorts is stopped after the first interim analysis). The posterior credible intervals of ORR when the observed ORR is in the range of 0-35% are summarized in Table JTJN.5.1. For illustrative purpose, the study drug will be considered active if ORR>25% and the uniform prior beta (1,1) is assumed in the Bayesian model. With the minimum sample size of N=20, the posterior probability of ORR exceeding 25% is <20% if the upper bound of 60% credible interval is <25%. With the maximum sample size of N=120, the posterior probability of ORR exceeding 25% is >80% if the lower bound of 60% credible interval is >25%.

The study efficacy may be monitored on an ongoing basis. The decision to close a cohort earlier may be made if results suggest the posterior probability of ORR exceeding the prespecified threshold of activity is well below 20%. The evaluation of the posterior probability of activity may occur before 20 patients are enrolled. For example, if the target response rate is 25%, under the uniform prior beta (1,1), the posterior probability that ORR is greater than 25% is only 13.3% if 0 response is observed out of 6 patients. If the target response rate is 15%, under the same prior, the posterior probability that ORR is greater than 15% is only 16.7% if 0 response is observed out of 10 patients.

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Table JTJN.5.1. Observed ORR and 60% Credible Interval

N=20			N=120		
Number of Responders	**Observed ORR**	**60% Credible Interval**	**Number of Responders**	**Observed ORR**	**60% Credible Interval**
0	0%	1.1%-7.4%	0	0%	0.2%-1.3%
1	5%	3.9%-13.6%	6	5%	3.9%-7.4%
2	10%	7.4%-19.3%	12	10%	8.3%-12.9%
3	15%	11.1%-24.7%	18	15%	12.8%-18.3%
4	20%	15.1%-29.9%	24	20%	17.4%-23.5%
5	25%	19.1%-35.0%	30	25%	22.1-28.7%
6	30%	23.3%-40.0%	36	30%	26.8%-33.8%
7	35%	27.6%-44.9%	42	35%	31.6%-38.9%

Abbreviations: ORR = overall response rate.

5. A Priori Statistical Methods

5.1. General Considerations

Statistical analysis of this study will be the responsibility of Lilly. The interpretation of study results will be the responsibility of the Lilly clinical research physician (CRP) / clinical research scientist (CRS) and the statistician. The Lilly CRP/CRS and the statistician will also be responsible for the appropriate conduct of an internal review process for both the final study report and any study-related material to be authorized for publication.

The primary analysis of the primary endpoint of overall response rate (ORR) will be performed when all enrolled patients have completed ≥2 months of follow-up and/or investigator-assessed best response assessments have been completed for all patients. All secondary endpoints will be evaluated at this time. Additional updated analyses of efficacy (including but not limited to time-to-event variables) and safety (including but not limited to adverse events) may be conducted at later times (approximately 10-18 months after last patient is enrolled) if deemed appropriate by the sponsor.

All confidence intervals (CIs) will be given at a 2-sided 95%, unless otherwise stated.

Unless otherwise specified, baseline for the time-to-event endpoints will be the date of enrollment (the date of assigning patients to a cohort) and baseline for the safety analysis will be the last assessable baseline prior to the dose administration.

Any change to the data analysis methods described in the protocol/SAP will require an amendment ONLY if it changes a principal feature of the protocol/SAP. Any other change to the data analysis methods described in the protocol/SAP, and the justification for making the change, will be described in the clinical study report. Additional exploratory analyses will be conducted as deemed appropriate.

5.2. Populations

The following analysis sets will be defined for this study:

Intent-to-Treat (ITT) population: will include all enrolled patients (i.e., patients have been assigned to a cohort). The ITT population will be used for all baseline, efficacy and PRO analyses.

Per-Protocol population: will include all treated patients who do not have any major protocol violations that could potentially affect the efficacy conclusions. This population will be used for efficacy and PRO sensitivity analyses.

Safety population: will include all enrolled patients who have received ≥1 dose of prexasertib, regardless of their eligibility for the study. This population will be used for all dosing/exposure, and safety analyses.

Pharmacokinetic population: will include all enrolled patients who have received ≥1 full dose of prexasertib and have baseline and ≥1 postbaseline evaluable PK sample.

Biomarker population: will include all enrolled patients from whom a valid assay result has been obtained.

5.3. Handling of Dropouts or Missing Data

Missing data, except dates, will not be imputed. Historical data such as historical diagnosis, historical illness, pre-existing conditions and prior therapies should be collected in a sufficiently informative way. For example, in order to be considered as historical illness, events occurring in the same year as study entry should have at least a known month and year for the end date, while events occurring in previous years should have at least a known year for the end date. When dates need to be imputed, missing days will be replaced with 15th of the month and missing day/month with 01 JULY.

5.4. Patient Disposition

Patient disposition will be summarized by cohort and overall. It will include a summary of the number and percentage of patients entered into the study, enrolled in the study, and treated, as well as number and percentage of patients completing the study (patients who receive ≥1 dose of study drug and have ≥1 post-baseline tumor assessment), or discontinuing (overall and by reason for discontinuation). Reason for discontinuation from both the study treatment and the study will be summarized by pre-determined categories.

5.5. Patient Characteristics

Patient demographics including age, race, ethnicity, country, screening height, weight and body surface area (BSA) will be reported using descriptive statistics.

Patient baseline disease characteristics including pathological diagnosis, disease stage, and Eastern Cooperative Oncology Group (ECOG) performance status will be summarized.

Patient preexisting condition, historical illness, prior anti-cancer therapies and other baseline characteristics such as smoking status will be summarized.

Patient characteristics will be summarized by cohort and overall.

5.6. Treatment Compliance

Treatment with prexasertib will be administered at the investigator site, therefore treatment compliance is assured.

5.7. Concomitant Therapy

All medications will be coded to the generic preferred name according to the current World Health Organization (WHO) drug dictionary. All concomitant medications will be summarized for the safety population using the preferred name by cohort and overall.

The use of analgesic medications will be summarized and listed, including dose, unit, frequency, and route of administration. Each analgesic may be analyzed according to the WHO pain ladder (WHO cancer pain relief, 1986) and/or the Analgesic Quantification Algorithm (AQA) (Chung et al. 2014). Additional exploratory analysis about the analgesic use may be conducted if deemed appropriate.

5.8. Post-Study-Treatment Therapy

The numbers and percentages of patients receiving post-study-treatment anticancer therapies will be provided by type of therapy (surgery, radiotherapy, or systemic therapy), and by drug class and/or name, overall and by line of therapy. The therapies will be summarized by cohort and overall for the safety population.

5.9. Efficacy Analyses

Efficacy analyses will be conducted on the ITT population and summarized by cohort. Efficacy analyses for interim analyses may be based on the safety population.

5.9.1. Primary Efficacy Analyses

Overall response rate (ORR) is defined as the number of patients who achieve a best overall response of complete response (CR) or partial response (PR) divided by the total number of enrolled patients per cohort. The ORR, with corresponding 95% exact CI, will be summarized for each cohort. The posterior estimates of ORR and posterior probability of ORR that is greater than the cutoff value will also be derived via a Bayesian model.

- Cohort 1, 2 and 3: posterior Pr (ORR>25%)
- Cohort 4: posterior Pr (ORR>15%)

Disease control rate (DCR) is defined as the number of patients who achieve a best overall response of CR, PR or stable disease for ≥4 months divided by the total number of enrolled patients per cohort. The DCR, with corresponding 95% exact CI, will be summarized for each cohort.

CA-125 response is defined as ≥50% reduction in CA-125 levels from a pretreatment sample. The response must be confirmed and maintained for ≥28 days according to GCIG criteria. Patients must have a pretreatment sample that is ≥2 times the upper limit of the reference range and obtained within 2 weeks before starting the treatment. The response rate based on CA-125, with corresponding 95% exact CI, will be summarized for each cohort.

Progression-free survival (PFS) is defined as the time from the date of enrollment until the first occurrence of documented disease progression per RECIST 1.1, or death from any cause in the absence of progressive disease (PD). Progression-free survival curves, median PFS, and PFS rates at 3 months intervals up to 12 months with 95% CI for each cohort will be estimated using the Kaplan-Meier (KM) method (Kaplan and Meier 1958).

If a patient is not known to have progressed or died at the time of analysis, PFS time will be censored at the last known progression-free assessment. The detailed censoring rules are described in Table JTJN.6.1.

Table JTJN.6.1. PFS events/Censoring Scheme

Situation[a]	Event/Censor	Date of Event or Censor
Tumor progression or death	Event	Earliest date of PD or death
No tumor progression and no death	Censored	Date of last adequate radiological assessment or date of randomization (whichever is later)[b]
Unless		
No baseline radiological tumor assessment available	Censored	Date of enrollment
No adequate postbaseline radiological tumor assessment available and death reported after missing 2 scan intervals following randomization[b,c]	Censored	Date of enrollment
Tumor progression or death documented immediately after missing 2 or more scan intervals following last adequate radiological tumor assessment or enrollment (whichever is later)[b,c]	Censored	Date of last adequate radiological assessment or date of enrollment (whichever is later)[b]
New anticancer therapy started before tumor progression or death	Censored	Date of last adequate radiological assessment prior to the start of new anticancer therapy or date of enrollment(whichever is later)[b]

Abbreviations: CR = complete response; PD = progressive disease; PFS = progression-free survival; PR = partial response; SD = stable disease.

a Symptomatic deterioration (that is, symptomatic progression that is not radiologically confirmed) will not be considered as tumor progression.

b Adequate radiological tumor assessment refers to an assessment with one of the following responses: CR, PR, SD, or PD.

c 2 scan intervals = 4 months.

Duration of response (DoR) is defined as the time from the date measurement criteria for CR or PR (whichever is first recorded) are first met until the first radiographic documentation of progression or death from any cause in the absence of PD. The analysis is for confirmed responders only. Median duration of response will be estimated using the KM method. The DoR will be censored according to the same rules as PFS.

Overall survival (OS) is defined as the time from the date of enrollment until death from any cause. If the patient is alive, lost to follow-up or withdrawn from study at the time of data analysis, OS data will be censored on the last date the patient is known to be alive. Overall survival curves, median overall survival, and survival rates at 6 months intervals up to 24 months with 95% CI for each cohort will be estimated using the KM method.

5.9.2. Sensitivity Analyses

Patients are assigned to cohorts based on the local *BRCA* results. Sensitivity analyses of the efficacy endpoints may be done based on the centrally confirmed *BRCA* results. Other sensitivity analyses may be conducted if deemed appropriate.

5.10. Health Outcomes/Quality-of-Life Analyses

Patient reported outcomes data is being collected via a site and home-based device. The schedules of the health outcome assessments are summarized below. Daily collection of the Worst Pain NRS via the home device will be discontinued at progression or after Day 28 of Cycle 6, whichever comes first.

Questionnaires administered in clinic	*Baseline visit*	*Administered on day 1 of each cycle, beginning with cycle 2*	*Short term follow-up*
Worst Pain NRS	x		x
NFOSI-18	x	X	x

At home	
Worst pain NRS	Daily at bedtime

For each questionnaire, the compliance rate will be calculated as the number of completed assessments divided by the number of expected assessments. The compliance rate for the Worst Pain-NRS will be calculated at baseline, per week and per cycle, with reasons for non-compliance to be collected and reported for the baseline and short-term follow-up visit only. Additionally, the proportion of patients who have completed ≥50% of daily Worst Pain NRS assessments in the 7-day period prior to the first dose of each cycle and during each consecutive 7 day period post-baseline will be computed at each cycle. Patients will be considered compliant if they have completed ≥50% of the daily assessments during each period (e.g., week, cycle). The number of expected assessments for each period is the number of patients who have received last scheduled study drug before the scheduled assessment days (e.g., patients who have received Day 1 drug should be expected to complete all daily assessments before they receive Day 15 drug). For the NFOSI-18, the compliance rate will be calculated at baseline, each post-baseline visit (starting with cycle 2), with reasons for noncompliance to be collected and reported for all visits. The number of expected assessments at each post-baseline visit (starting with cycle 2) is the number of patients who have received study drug in a previous cycle.

For the Worst Pain NRS, a 7-day average of scores prior to the first dose of each cycle and a rolling 7-day average of scores regardless of dosing will be computed if ≥50% assessments are completed during each period. A 7-day average of scores based on any available data may be computed for sensitivity analysis even if compliance is less than 50%. For the NFOSI-18, the total score will be computed at baseline, each cycle (starting with cycle 2), and short term follow-up along with scores for the Disease Related Symptoms-Physical subscale, the Disease Related Symptoms-Emotional subscale, the Treatment Side Effects subscale, and the Function/Well-Being subscale.

Change from baseline for pre-specified concepts of interest (worst pain and NFOSI Total Score and Subscales) will be descriptively analyzed. For the Worst Pain NRS, change from baseline will be assessed in the 7-day average prior to the first dose of each cycle.

Time to deterioration in the total score as well as specific subscales and items in the NFOSI-18 is defined from the time of the patient's baseline visit to the time of the first increase in the respective score with confirmation at the next consecutive cycle or death from any cause, whichever comes first (a threshold characterizing meaningful worsening will be determined based on forthcoming psychometric analyses). Time to pain progression based on Worst Pain NRS and the weekly average of the worst pain scores will also be assessed. Median time to pain progression/deterioration with 95% CI for each cohort will be estimated using the KM method. Data for cohorts that have stopped early may not be analyzed. Correlation analysis between NFOSI pain item and the worst pain NRS will be conducted to account for lack of NRS data after cycle 6.

Data on analgesic consumption will be analyzed independently as well as in conjunction with PRO data from the worst pain NRS. For example, patients with pain progression based on worst pain NRS and their analgesic consumption will be summarized.

The association between PRO measures and efficacy outcomes may also be explored if deemed appropriate.

5.11. Pharmacokinetic/Pharmacodynamic Analyses

Pharmacokinetic (PK) and pharmacodynamic analyses will be performed according to a separate PK analysis plan.

5.12. Biomarker Analyses

The biomarkers of interest (e.g., *BRCA* status based on the local or central lab) will be summarized. The association between biomarkers and clinical outcomes will be explored. Further exploratory analysis of biomarkers may be conducted if deemed necessary and a sufficient number of patients who express the biomarker(s) are available.

5.13. Safety Analyses

Safety analyses will be based on the safety population. Safety analyses will be summarized by cohort and overall.

5.13.1. Extent of Exposure

Study drug exposure information will be summarized by cohort and overall, including cycles received per subject, duration on therapy, cumulative dose (mg/m^2), dose intensity and relative dose intensity.

Prexasertib will be administered as an intravenous infusion on Day 1 and 15 of a 28-day cycle. Duration on therapy is calculated as the last dosing date+14-first dosing date. Dose intensity of prexasertib (mg/m^2/week) is calculated as cumulative dose/ duration on therapy in weeks. Relative dose intensity of prexasertib is calculated as actual dose intensity per week/planned dose intensity per week ×100, where planned dose intensity per week=(105/2) mg/m^2/week.

Dose adjustments, delays and omissions, along with the reasons, will be summarized and listed.

5.13.2. Adverse Events

Adverse event (AE) verbatim terms will be provided by the investigators and then will be mapped by Lilly or its designee to corresponding terminology within the Medical Dictionary for Regulatory Activities (MedDRA) Lower Level term (LLT) dictionary. The investigator will use Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (NCI 2009) to assign AE severity grades.

Pre-existing conditions are defined as AEs that begin but do not resolve prior to the first dose of study drug in each study period. Pre-existing conditions will be presented by patient and can be combined with the listing of AE, so that the history of the pre-existing conditions/AEs can be traced.

A treatment emergent adverse event (TEAE) is defined as any AE that begins on or after the day of first dose in the reporting study period or any pre-existing condition that increases in CTCAE grade on or after the day of first dose in the reporting study period. The MedDRA LLT will be used in the treatment-emergent computation.

The number of patients who experienced a TEAE, or TEAE possibly related to study drug, will be summarized. Treatment-emergent adverse events will be summarized by SOC, by Preferred Term (PT) of decreasing frequency within SOC, and by maximum CTCAE grade and grade categories (any, Grade 3 or higher).

5.13.3. Deaths, Serious Adverse Events, Other significant Adverse Events

All deaths that occur during the study, within 30 days of the study treatment discontinuation, as well as the cause of death, will be summarized and listed.

Serious adverse events (SAEs) are those events that result in death, are life-threatening, require or prolong hospitalization, result in persistent or significant disability/incapacity, or cause congenital anomaly/birth defect. Serious adverse events will be tabulated by SOC, PT terms, and relationship to study drug.

5.13.4. Clinical Laboratory Evaluation

All relevant hematology and chemistry laboratory values will be graded according to CTCAE Version 4. Shift tables showing the change from baseline to the worst grade on study will be presented.

5.13.5. Vital Signs and Other Physical Findings

Temperature, blood pressure, pulse rate, weight and ECOG performance score will be summarized by cohort and overall.

5.13.6. Electrocardiograms

Local electrocardiograms (ECGs) will be summarized by cycle and overall. The summary by cycle will classify patients as having normal or abnormal. Additionally, QT, RR, and QRS

intervals will also be collected and QTcF will be calculated based on these parameters. Adverse events that could be associated with abnormal ECGs will be presented, if appropriate.

5.13.7. Healthcare Resource Utilization

The frequency and percentage of patients with hospitalizations, transfusions, ED visits experienced during the study treatment period or 30-day post discontinuation follow-up period will be summarized.

5.14. Protocol Violations

Significant protocol violations that potentially compromise the data integrity and patients' safety will be summarized by cohort and overall. These violations will include deviations which can be identified programmatically and those which can only be identified by the clinical research associate (CRA) during monitoring. Significant protocol deviations are described in another document within the study Trial Master File.

5.15. Interim Analyses

Interim analyses will be conducted regularly to evaluate closing enrollment early due to futility. For each cohort, the first futility interim analysis will be conducted after approximately 20 patients have been treated and completed ≥2 cycles or have discontinued before the first post-baseline tumor assessment. The interim analysis may be potentially delayed if the confirmation of response is required. The futility rule is based on the posterior probability of activity via a Bayesian model. A cohort will be closed if the posterior probability is less than the prespecified futility threshold (e.g., 20% probability ORR exceeds the prespecified threshold of activity). Borrowing of information across cohorts may be allowed, and the strength of borrowing may depend on the similarity between the cohorts. The prior distribution of response rate used in the model will be derived from the ongoing NCI-sponsored Phase 2 Study E001 (NCT02203513). The futility rules for each cohort are described as follows:

- Cohorts 1 to 3 (platinum-resistant): Pr (ORR>25%) <20%
- Cohort 4 (platinum-refractory): Pr (ORR>15%) <20%.

It is planned that enrollment can continue while interim analyses are conducted, but the sponsor may decide to pause the enrollment, if necessary. For the cohorts that can continue after the evaluation of the first 20 patients, subsequent interim analyses will occur after approximately every 20 additional patients. The interval between interim analyses may be adjusted if deemed appropriate based on enrollment rates and available data. At each subsequent interim for each cohort, the posterior probability of response rate will be updated based on the available data and a higher futility threshold for the posterior probability may be adopted if deemed appropriate by the sponsor (e.g., 40% probability ORR exceeds the prespecified threshold of activity).

At each interim analysis, although the decision of whether to continue a cohort will be made primarily based on the futility rules, the totality of data (including safety, efficacy, PK, and biomarker data, if available) will also be reviewed and considered in the final decision made by the sponsor. The decision will be communicated to sites in writing if the sponsor determines a

cohort is to be closed. The evaluation of efficacy may be based on all treated patients with centrally confirmed *BRCA* mutation status if available. Other interim analyses may be conducted if deemed appropriate by the sponsor. The interim analyses may be combined if they are expected to occur within a similar timeframe; interim analyses may also be combined with any prespecified safety review or annual reporting (such as an update to the IB or Development Safety Update Review, etc.).

5.16. Annual Report Analyses

The following reports are needed as requested for annual reporting purposes.

Development Safety Update Report:

- Cumulative Subject Exposure by Age Group and Sex
- Cumulative Subject Exposure by Racial Group
- Estimated Cumulative Subject Exposure
- Exposure Information
- Listing of Discontinuations Due to AE During the Reporting Period
- Listing of Subjects Who Died During the Reporting Period

Clinical Investigator's Brochure (IB):

- Listing and Summary of SAE
- Listing and Summary of Death
- Listing and Summary of TEAE (and by maximum CTCAE grade)
- Listing and Summary of Patient Disposition
- Listing and Summary of Study Drug Adjustment

Other reports may be requested if deemed appropriate for the IB.

5.17. Clinical Trial Registry Analyses

Additional analyses will be performed for the purpose of fulfilling the Clinical Trial Registry (CTR) requirements.

Analyses provided for the CTR requirements include the following:

- Summary of AEs, provided as a dataset which will be converted to an XML file. Both SAEs and 'Other' AEs will be summarized by: MedDRA PT within treatment group.
- An AE is considered 'Serious' whether or not it is a TEAE.

- An AE is considered in the 'Other' category if it is both a TEAE and is not serious. For each SAE and 'Other' AE, for each term and treatment group, the following are provided:
  - the number of participants at risk of an event
  - the number of participants who experienced each event term
  - the number of events experienced.
- Consistent with www.ClinicalTrials.gov requirements, 'Other' AEs that occur in fewer than 5% of patients/subjects in every treatment group may not be included if a 5% threshold is chosen (5% is the minimum threshold).
- Adverse event reporting is consistent with other document disclosures for example, the clinical study report (CSR), manuscripts, and so forth.

In addition, a participant flow will be created that will describe how many enrolled patients completed the study, and for those who did not, the frequency of each reason for not completing. This analysis will be based on study discontinuation, not treatment discontinuation. A patient will be identified as having completed the study if the patient has received ≥1 dose of study drug and have ≥1 post-baseline tumor assessment at the time of the final analysis.

6. References

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