Protocol C3441020

A Phase 2, Non-randomized, Open Label, Single arm, Multi-center Study of Talazoparib for Neoadjuvant Treatment of Germline BRCA1/2 Mutation Patients with Early Human Epidermal Growth Factor Receptor 2 Negative Breast Cancer

Statistical Analysis Plan (SAP)

Version: 3

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1. VERSION HISTORY

The Statistical Analysis Plan (SAP) for study C3441020 is based on the protocol approved 14AUG2019.

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 12 Feb 2019	Amendment 3 16 Nov 2018	N/A	N/A •
2 23 Sep 2019	Amendment 4 14 Aug 2019	Changed to reflect study changes included in Amendment 4	• In study population: "triple negative breast cancer" changed to "human epidermal growth factor receptor 2 negative breast cancer" • Changed Study Design section • Added details on RCB • Updated Analysis Sets definitions • Updated Sample Size Determination and Statistical Decision Rules section • Added clarifications in the Quality of Life section 6.3 for EORTC QLQ-C30, EORTC QLQ-BR23 CCI [redacted] • Updated Section 7 on Interim Analysis
3 26 Feb 2020		Changes to incorporate an analysis requested by the FDA plus other minor refinements to definitions	• Added sensitivity analysis of pCR when the local BRCA test is positive for gBRCA1/2 mutation and the central Myriad BRACAnalysis test is negative • Refined algorithm for calculation of RDI • Added definition of Evaluable Population as per Investigator assessment • Other minor clarifications and refinements

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in study C3441020. This analysis plan is meant to supplement the study protocol. Any deviations from this analysis plan will be described in the Clinical Study Report.

Talazoparib is a potent, orally bioavailable, small molecule PARPi in development for the treatment of a variety of human cancers. Single agent talazoparib treatment demonstrates potent antitumor effects in tissue culture studies, mouse tumor xenograft models, and in Phase 1 studies in patients with solid tumors. Talazoparib has also been shown to enhance the cytotoxic effects of DNA damaging chemotherapy.

The current Phase 2 study provides the opportunity to evaluate the safety and efficacy of talazoparib in the neoadjuvant setting for patients with early gBRCA1/2 mutation positive, HER2 negative breast cancer. It will also evaluate patient reported outcomes CCI [redacted] n this patient population.

2.1. **Study Objectives**

Primary Objective:

- To evaluate the pathological complete response (pCR) following treatment with talazoparib after completion of 24 weeks of neoadjuvant therapy followed by surgery. pCR will be assessed by Independent Central Review (ICR).

Secondary Objectives:

- To evaluate pCR (breast and axilla) by investigator (INV)
- pCR in breast only (ICR and INV);
- Residual cancer burden (RCB) by ICR;
- To evaluate long term outcome by assessment of 3 years event-free survival (EFS) and overall survival (OS);
- To evaluate the safety and tolerability of talazoparib;
- To describe the steady-state pharmacokinetics (PK) of talazoparib in patients with germline breast cancer susceptibility gene (gBRCA) mutation-positive, HER2 negative breast cancer.
- To evaluate the following patient reported outcomes (PRO):
  - Global health status/Quality of Life (QoL), functioning, and symptoms (including nausea and vomiting);
  - Missed expected menstrual period; this objective captures the concept of fertility preservation through PRO, since there is a possible fertility sparing effect of talazoparib versus chemotherapy.

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2.2. **Study Design**

This is a non-randomized, phase 2, single-arm, open-label, multi-center study enrolling patients with gBRCA1/2 mutation positive HER2 negative breast cancer. Sixty patients in total will be enrolled in the study and treated with talazoparib 1 mg QD for 24 weeks followed by surgery. With a sample size of 60 patients, the two-sided 80% exact Blaker confidence interval (CI) for the pCR rate would be at most 17% wide. If a pCR=50% is observed, the lower bound of the exact 80% CI would exclude 41%.

An interim futility analysis, designed based on Bayesian predictive probability (PP), will be conducted once 28 evaluable patients as per ICR are assessed for pCR. The PP is the probability of concluding a positive result by the end of the trial based on the cumulative information in the current stage. The trial will be considered a success if the posterior probability that the true pCR rate exceeds 45% is ≥80%. Predictive probability <10% was set as the futility boundary and assumed a non-informative beta (1,1) prior. Once 28 evaluable patients as per ICR are assessed for pCR, if 11 responses or less are observed, the predictive probability of the trial being successful at the full sample size is less than 10%, at which point the Sponsor would recommend stopping the study due to futility. If ≥12 responses are observed in the first 28 evaluable patients per ICR, the study will continue enrolling to 60 patients.

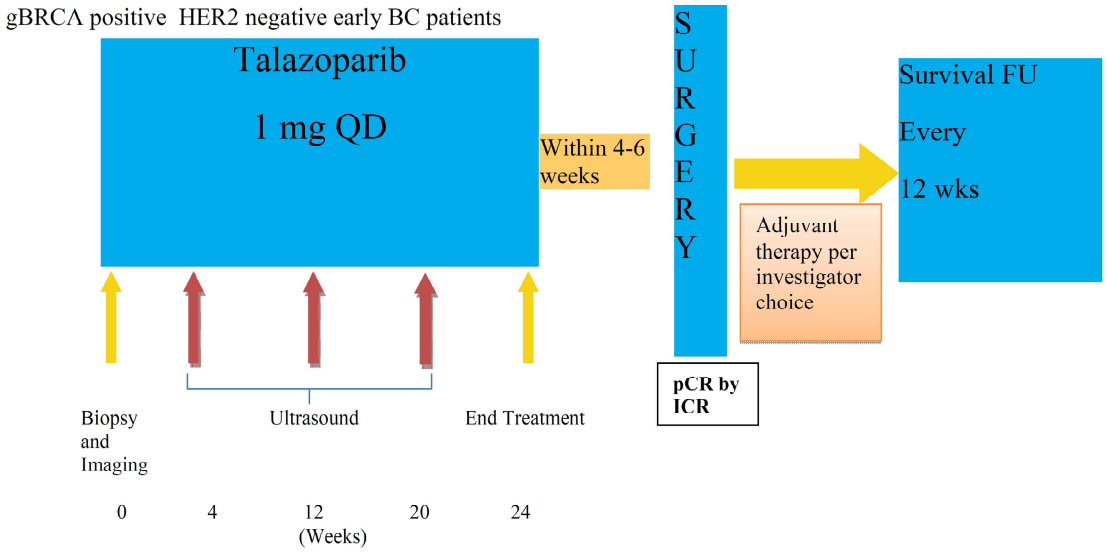
The evaluable population as per ICR is the primary analysis population at the interim and final analysis. Patients that do not complete 80% of the talazoparib dose prescribed at treatment start for 24 weeks, do not have surgery, or for whom the ICR assessment of the postsurgery specimen is not available, will be excluded from the evaluable population as per ICR (unless they progressed or died before pCR could be assessed). Patients who die or progress before pCR could be assessed will be included as non-responders in the analyses. The ITT population will include all patients who received any amount of talazoparib, regardless of whether or not they are considered evaluable as per ICR.

A patient will participate in up to 4 periods: screening, talazoparib treatment phase, safety follow-up, and long-term follow-up. Patients will be evaluated at screening for the presence of a deleterious, suspected deleterious or pathogenic germline BRCA1 or BRCA2 mutation as confirmed by a local CLIA (Clinical Laboratory Improvement Amendments) certified test. Patients must also consent to a blood sample for central genomic assessment using the BRACAnalysisCDx test by Myriad Genetics, except for patients who already have evidence of BRCA1/2 mutation by MYRIAD BRCAnalysisCDx post 2016. Long-term follow up period is at least 5 years, which starts from the date of surgery for EFS and after first dose of drug for OS. Figure 1 provides a study schematic.

End of treatment visit will occur 28 days after the last dose of study drug or before initiation of a new antineoplastic or investigational therapy, whichever occurs first. Safety follow-up begins from the time of first dose of study drug through and including a minimum of 28 calendar days after the last administration of study drug or surgery, whichever occurs later.

There will also be an additional post- surgical safety follow up, 4 weeks after surgery for assessment of wound healing.

Figure 1. Study Schematic: Single Agent Talazoparib



Target Enrollment: **n=60**

Key Criteria:

- Tumor ≥T1, N0-3;
- No evidence of distant metastasis;
- Early HER2 negative BC;
- gBRCA mutation-positive;
- No previous or concomitant anti- cancer therapies used for the treatment of cancer in the last 3 years;
- Prior surgical treatment for contralateral DCIS allowed.

Abbreviations: gBRCA= germline mutation of breast cancer susceptibility gene; HER2= human epidermal growth factor receptor 2; BC=breast cancer; mg=milligram; QD=once a day; FU=follow-up; pCR=pathological complete response; ICR=independent central review; DCIS=ductal in situ carcinoma.

3. ENDPOINTS AND COVARIATES

3.1. Primary Endpoint

- **Pathological Complete Response (pCR)** is defined as the absence of invasive cancer in the breast and axillary lymph nodes on hematoxylin and eosin evaluation of the complete resected breast specimen and all sample regional lymph nodes following completion of neoadjuvant systemic therapy (ie, ypT0/Tis ypN0 in the current AJCC staging system).

  pCR rate by ICR is defined as the percentage of patients achieving pCR by independent central review after talazoparib treatment for 24 weeks, followed by surgery, among all patients in the evaluable population by ICR.

3.2. **Secondary Endpoints**

pCR rate by investigator is defined as the percentage of patients achieving pCR by investigator review after talazoparib treatment for 24 weeks, followed by surgery, among all patients in the evaluable population by INV.

The *residual cancer burden* (RCB) by ICR is a four-category index derived from primary tumor dimensions, cellularity of the tumor bed, axillary nodal burden and is reported as RCB 0 (pCR), I (minimal RCB), II (moderate RCB), III (extensive RCB).

pCR rate in breast by ICR is defined as the percentage of patients achieving pCR in breast by independent central review after talazoparib treatment for 24 weeks, followed by surgery, among all patients in the evaluable population by ICR (ie, ypT0/Tis in the current AJCC staging system).

pCR rate in breast by investigator review is defined as the percentage of patients achieving pCR in breast by investigator review after talazoparib treatment for 24 weeks, followed by surgery, among all patients in the evaluable population by INV (ie, ypT0 in the current AJCC staging system).

EFS is defined as the time from surgery date to first documentation of local or distant recurrence of the same tumor type or death or initiation of antineoplastic therapy before documentation of first relapse. Patients discontinuing study before documentation of first relapse or death, but after surgery will be censored at the date of discontinuation for EFS.

Overall survival (OS) is defined as the time from first dose of talazoparib to death due to any cause. Patients not known to have died at the time of the analysis will be right censored on the date they were last known to be alive before the analysis data cutoff date.

Type, incidence, severity (as graded by National Cancer Institute [NCI] Common Terminology Criteria for *Adverse Events* [CTCAE] v4.03), seriousness and relationship of study medication to adverse event (AE) and any laboratory abnormalities.

Time to definitive deterioration of patient-reported global health status/QoL per EORTC (European Organisation of Research and Treatment of Cancer) QLQ (Quality of Life Questionnaire)-C30 is defined as >10 points decrease from baseline, cycle 1 day 1 visit, without any subsequent <10 points decrease through end of treatment visit.

Time to definitive deterioration of patient-reported nausea and vomiting symptoms per EORTC QLQ-C30 is defined as >10 points increase from baseline, cycle 1 day 1 visit, without any subsequent <10 points increase through end of treatment visit.

Change from Baseline in Global Health Status/Qol, Functioning, and Symptoms per EORTC QLQ-C30 and EORTC QLQ BR-23.

Change from baseline in proportion of patients with missed expected menstrual period per PRO-CTCAE.

Proportion of patients with deterioration, improvement, and no change in nausea and vomiting symptoms.

PK of talazoparib using sparse sampling (through concentrations [C_{trough}] at limited timepoints).

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3.4. **Safety Data**

Safety endpoints include adverse events (graded according to the NCI Common Toxicity Criteria for Adverse Events (NCI CTCAE, version 4.03), physical examination (including blood pressure and pulse rate), and laboratory tests (hematology, chemistry, and vital signs).

The safety of talazoparib will be evaluated by the analysis of incidence of serious and non-serious adverse events (AEs) and deaths, severity of adverse events, incidence of dose modifications and of permanent treatment discontinuation due to adverse events, and incidence of new clinically significant changes in clinical laboratory values and vital signs.

Adverse events will be coded to preferred term and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA) and classified by severity using the CTCAE, version 4.03.

Baseline tumor-related signs and symptoms will be recorded at the Cycle 1 Day 1 visit and then reported as AEs during the trial if they worsen in severity or increase in frequency.

Adverse events (AEs), hematology, blood chemistry will be assessed as described in the Schedule of Activities of the protocol beginning when the subject provides informed consent.

Patients who start treatment are assessed for toxicities up to 28 days after the date of permanent discontinuation from study or before initiation of new antineoplastic or investigational therapy (whichever comes first).

3.4.1. Treatment Emergent Adverse Event

An adverse event is considered treatment emergent if:

- The event occurs for the first time after the start of study treatment and before 28 days after the date of permanent discontinuation from treatment or before start of new antineoplastic therapy or investigational therapy, whichever occurs first.
- The event was seen prior to the start of treatment but increased in CTCAE grade during study treatment.
- Disease progression is not considered a treatment emergent adverse event unless the patient dies of disease prior to 28 days after discontinuation of treatment.

3.4.2. Treatment Related Adverse Event

Adverse events defined as treatment emergent adverse events related to treatment are judged by the investigator. Events that are continuation of baseline abnormalities are not considered treatment related unless there is an increase in grade, or if there is an increase following a decrease, and the increase is judged by the investigator to be caused by the treatment.

3.4.3. Laboratory Safety Assessments

Laboratory assessment will be assigned to cycles based on the collection date of the sample relative to the start dates of cycles from the study drug administration as described in the Schedule of Activities table in Appendix 10.1.

Baseline evaluations for laboratory are those collected

- Within 28 days prior to or on first day of study drug and
- If there is more than one baseline evaluation, closest to but any time prior to the 1st dosing on the first day of study treatment.

Laboratory values will be classified by severity using the CTCAE, version 4.03. Laboratory shift tables of baseline to maximum post-baseline grade will be produced.

Blood tests that will be analyzed are presented in Table 1.

Table 1 Laboratory Tests

Hematology	Chemistry	Additional
Hematocrit	Albumin	CCI [redacted]
Hemoglobin	Total protein	
Mean corpuscular volume	Alkaline Phosphatase	
RBC	ALT	
Platelets	AST	
	Total Bilirubin [a]	
WBC with differential	BUN	
ANC [b]	Creatinine	
Lymphocytes	Glucose (non-fasting)	
Monocytes	Bicarbonate	
Eosinophils	Calcium	
Basophils	Chloride	
	Magnesium	
	Phosphate	
	Potassium	
	Sodium	
	LDH	

[a] For potential Hy's law cases, in addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/INR, and alkaline phosphastase.

[b] If done locally and ANC is not provided, enter neutrophil and neutrophil band counts in CRF.

3.4.4. Other Safety Assessment

A full physical examination including an examination of all major body systems (including general appearance, head, ears, eyes, nose, mouth, throat, skin, heart, lung, lymph nodes, gastrointestinal, genitourinary, neurologic, and skeletal) per standard of care at the study site or as clinically indicated by symptoms may be performed by a physician, registered nurse or other qualified health care provider, will be required at screening, Day 1 of each cycle, Day 15 of Cycles 1 and 2, and end of treatment visit. A clinical exam of breast and axilla should be included in each physical exam. Vital sign measurements (blood pressure, heart rate, and temperature) and weight will also be assessed at the same visits. Height will also be measured at screening. Performance Status: The Eastern Cooperative Oncology Group (ECOG) performance status scale will be used at screening, Day 1 of each cycle, and end of treatment visit.

Imaging data from ultrasound scans will be collected at screening and on Day 1 of Cycles 2, 4 and 6. A summary table of new growth in organs by location will be provided.

3.5. **Other Endpoints**

3.5.1. Pharmacokinetic Data

Plasma PK samples for talazoparib determination will be collected at Cycle 2 Day 1, Cycle 3 Day 1, and Cycle 4 Day 1. Patients must be instructed to withhold their daily dose of talazoparib on PK sampling days until the pre-dose PK sample and safety assessments (i.e., hematology, blood chemistry) have been completed. The exact time of the sample collection and the most recent dosing time will be recorded on the CRF. The date of any missing dose(s) should also be recorded in the CRF.

The actual times may change but the number of samples will remain the same. All efforts will be made to obtain the pharmacokinetic samples at the exact nominal time relative to dosing.

4. ANALYSIS SETS

4.1.1. Evaluable Population according to ICR

The evaluable population according to ICR is defined as all patients enrolled in the study who receive at least 80% of the dose of talazoparib prescribed at treatment start (1 mg/day of talazoparib, with the exception of patients with baseline moderate renal impairment who will receive a starting dose of 0.75 mg/day of talazoparib) , undergo breast surgery and pCR assessment, as well as those patients who progress or die before pCR can be assessed. Patients who receive less than 80% of the dose of talazoparib prescribed at treatment start during the neoadjuvant treatment period, do not have surgery, or for whom the ICR assessment of the post-surgery specimen is not available, will be excluded from the evaluable population (unless they progressed or died before pCR could be assessed).The evaluable population will be the primary population for evaluating all efficacy endpoints at interim analysis as well as the final analysis. Patients who progress or die before pCR can be assessed by ICR will be considered as non-responders in the evaluable population per ICR.

4.1.2. Evaluable Population according to INV

The evaluable population according to INV is defined as all patients enrolled in the study who receive at least 80% of the dose of talazoparib prescribed at treatment start (1 mg/day of talazoparib, with the exception of patients with baseline moderate renal impairment who will receive a starting dose of 0.75 mg/day of talazoparib) , undergo breast surgery and pCR assessment, as well as those patients who progress or die before pCR can be assessed. Patients who receive less than 80% of the dose of talazoparib prescribed at treatment start during the neoadjuvant treatment period, do not have surgery, or for whom the INV assessment of the post-surgery specimen is not available, will be excluded from the evaluable population (unless they progressed or died before pCR could be assessed). Patients who progress or die before pCR can be assessed by investigator will be considered as non-responders in the evaluable population per INV.

4.2. **Intent-to-treat (ITT) Analysis Population**

The ITT analysis population is defined as all patients who receive any amount of talazoparib. All efficacy analyses will also be reported in the ITT analysis population, unless otherwise specified.

4.3. **Other Analysis Sets**

4.3.1. Safety Population

The Safety analysis population is defined as all patients who receive any amount of talazoparib and is the same as the ITT analysis population. All safety analyses will be performed using the safety population.

4.3.2. Pharmacokinetic Analysis Population

The PK analysis population is defined as all patients treated with talazoparib for whom drug plasma concentration results (from at least 1 visit) are available. For the PK analysis population, talazoparib concentration will be summarized descriptively by nominal time and talazoparib dose strength. Additionally, a subgroup of PK samples which meet pre-defined stead-state acceptance criteria will be summarized by nominal time and a within-patient average talazoparib steady state trough concentration will be listed by patient from this population.

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4.3.4. Patient Reported Outcome Analysis Population

The PRO analysis population is defined as all patients who completed a baseline and at least one post baseline quality-of-life assessment prior to the end of the study treatment.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. **Statistical Hypotheses**

The primary objective of this study is to evaluate the pCR by ICR after completion of 24 weeks of neoadjuvant therapy followed by surgery. This study is designed to test the null hypothesis that the true pCR rate is 35%.

5.2. **Sample Size Determination and Statistical Decision Rules**

Sixty patients will be enrolled in the study and treated with talazoparib 1 mg QD for 24 weeks followed by surgery. With a sample size of 60 patients, the two-sided 80% exact

Blaker CI for the pCR rate would be at most 0.17 wide. If a pCR=50% is observed, the lower bound of the exact 80% CI would exclude 41%.

An interim futility analysis, designed based on Bayesian PP, is planned after 28 evaluable patients per ICR are assessed for pCR. The PP is the probability of concluding a positive result by the end of the trial based on the cumulative information in the current stage. The trial will be considered a success if the posterior probability that the true pCR rate exceeds 45% is ≥80%. Predictive probability <10% was set as the futility boundary and assumes a non-informative Beta (1,1) prior. Once 28 evaluable patients are assessed for pCR, if 11 responses or less are observed, the predictive probability of a successful trial at the full sample size is less than 10%, at which point the Sponsor would recommend stopping the study due to futility. If ≥12 responses are observed in the first 28 evaluable patients, the study will continue enrolling to 60 patients.

In the HR positive group after 6 evaluable patients have completed treatment and undergone surgery, the pCR rate will be assessed. If 2 patients achieve pCR out of the initial 6, then the posterior probability that the true pCR rate in the HR positive group is greater than 45% would be 28.9%, assuming a non- informative Beta (0.5,0.5) prior. Therefore, if 2 or more pCRs are observed, the HR positive subgroup will continue to enroll. If 1 or no pCRs are observed, then closing of the HR positive subgroup will be considered. In the event that enrollment in the HR positive group is stopped, enrollment in the TNBC group will continue to a total of 60 patients assuming the overall trial has not been stopped for futility.

5.3. **General Methods**

5.3.1. Analyses for Time-to-Event Data

Time-to-event endpoints will be summarized using the Kaplan-Meier method and displayed graphically when appropriate. Median event times and 2-sided 95% confidence interval for median will be provided.

5.3.2. Analyses of Binary Data

Point estimates of the rates will be provided along with the corresponding exact 2-sided 95% confidence intervals using the exact method based on Blaker method.

5.3.3. Analyses of Multinomial Data

Point estimates of the RCB will be provided along with the corresponding exact 2-sided 95% confidence intervals using the exact method based on Goodman's method.

5.3.4. Analyses of Continuous Data

Descriptive statistics, including the n, mean, standard deviation, median, minimum, and maximum values, will be provided for continuous endpoints. Descriptive statistics for biomarkers will include %CV.

5.3.5. Analyses for Categorical Data

The number and percentage of patients in each category will be provided for categorical variables.

5.4. Handling of Missing Values

5.4.1. Missing Dates

In compliance with Pfizer standards, if the day of the month is missing for any date used in a calculation, including determining whether a medication is prior or concomitant, the 1st of the month will be used to replace the missing date unless the calculation results in a negative time duration (e.g., date of onset cannot be prior to day one date). In this case, the date resulting in 1 day duration will be used. If the day of the month and the month are missing, January 1 will be used to replace the missing date. For stop dates, the last day of the month, or last day of the year is used if the day or day and month are missing, respectively.

Missing dates for adverse events will be imputed based on the similar principle.

- For the start date, if the day of the month is missing, the 1st day of the month will be used to replace the missing date. If both day and month are missing, January 1 of the non-missing year will be used to replace the missing date. If the first dose date is later than this imputed date, then impute the start date again to the first dose date.
- For the stop date, if the day of the month is missing, the last day of the month will be used to replace the missing date. If both day and month are missing, December 31 of the non-missing year will be used to replace the missing date.

If the start date is missing for an AE, the AE is considered to be treatment emergent unless the collection date is prior to the treatment start date.

No imputation will be done for first dose date of study drug. If the last date of study drug is completely missing and there is no End of Treatment (EOT) date and no death date then the cutoff date will be used for the analysis as the last dosing date. If the day and month of last date of study drug is missing, then impute December 31 of non-missing year. Impute the last day of the month when month and year are non-missing. If the non-missing portion of the date is greater than the EOT date or death date, then impute the minimum of these two dates.

If the start date of new anti-cancer therapy is completely or partially missing, then the imputed start date of new anti-cancer therapy is derived as the recurrence date plus 1 day. When the non-missing year of start of new therapy is less than the year of recurrence, and if the day and month are missing then impute December 31 of non-missing year. Impute the last day of the month when month and year are non-missing. When the non-missing year of start of new therapy is greater than the year of progression, and if the day and month are missing then impute January 1 of non-missing year. Impute the first day of the month when month and year are non-missing.

5.4.2. Missing Assessments

Inadequate baseline assessment may include

- Not all required baseline assessments were done
- Assessments were done outside the required window

Follow-up visit for assessment of new lesions to determine EFS.

5.4.3. Missing Patient Reported Outcome Data

For the EORTC QLQ-C30 and EORTC QLQ BR-23, in cases where two answers are given to one item, the more severe answer will be counted. If at least half of the constituent items for the multi-item functional or symptom scale have been answered, then the score for that scale may be pro-rated based on the non-missing items. For subsequent analysis purposes, missing items will be considered missing; they will not be imputed.

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6. ANALYSES AND SUMMARIES

All efficacy analyses will be conducted on the evaluable population. All efficacy analyses will also be reported in the ITT analysis population, unless otherwise specified. All analyses will be performed by using SAS® Version 9.4 or higher.

6.1. Primary Efficacy Analysis

pCR rate by ICR in the evaluable population will be analyzed at the time of the interim and final analyses and will be summarized along with the exact 80% and 95% CI. Repeated confidence intervals may also be calculated.

pCR rate by ICR will also be summarized in the ITT population along with exact 80% and 95% CI. Patients who discontinue treatment or study prematurely, are lost to follow-up, withdraw consent, progress or die before pCR can be assessed by central review will be considered as non-responders in the ITT population.

For all patients, study drug treatment should continue until completion of protocol assigned therapy, followed by surgery unless the patient is no longer clinically benefitting in the opinion of the investigator, there is unacceptable toxicity, withdrawal of consent, or death.

Dosing interruptions are permitted for a period of 28 days to allow recovery from drug related toxicities.

If a patient receives less than 80% of the protocol required treatment, undergoes surgery and achieves pCR by ICR, the patient will be counted as responder in the ITT population, but not in the evaluable population.

pCR rate by ICR will be shown also by BRCA1/BRCA2 status.

6.2. **Secondary Analyses**

6.2.1. Pathological Complete Response by Investigator Review

pCR rate by investigator in the evaluable by INV population will be analyzed at the time of the interim and final analyses and will be summarized along with the exact 95% CI.

pCR by investigator will also be summarized in the ITT population, along with the exact 95% CI. Patients who discontinue treatment or study prematurely, are lost to follow-up, withdraw consent, progress or die before pCR can be assessed by investigator will be considered non-responders in the ITT population.

If a patient receives less than 80% of the protocol required treatment, undergoes surgery and achieves pCR by investigator review, the patient will be counted as a responder in the ITT population, but not in the evaluable by INV population.

6.2.2. Sensitivity analysis of pCR (when the local BRCA test is positive for gBRCA1/2 mutation and the central Myriad BRACAnalysis test is negative)

Impact of discrepancies between local BRCA and central Myriad BRCA assessment of gBRCA1/2 mutation status will be investigated with

- a 2x2 table of gBRCA1/2 mutation status by local BRCA test vs central Myriad BRCA
- In case there are patients positive for local BRCA test and not for central Myriad BRCA, a sensitivity analysis evaluating pCR per ICR in an additional population obtained excluding those without positivity for central Myriad BRCA will be done
- In case there are patients positive for local BRCA test and not for central Myriad BRCA, a sensitivity analysis evaluating pCR per INV in an additional population obtained excluding those without positivity for central Myriad BRCA will be done

6.2.3. Residual Cancer Burden

Residual cancer burden by ICR in the evaluable population will be reported as a categorical variable with four classes (categories) RCB 0 (pCR), I (minimal RCB), II (moderate RCB), III (extensive RCB).

Number and percentage of patient for all 4 categories in the evaluable population will be reported along with exact 95% CI as per Goodman's method. The analysis of RCB by ICR will be conducted in the evaluable population.

6.2.4. Pathological Complete Response in Breast by Independent Central Review and Investigator

pCR in breast rate in the evaluable population will be summarized using descriptive statistics along with the exact 95% CI.

pCR in breast rate will also be summarized in the ITT population along with exact 95% CI. Patients who discontinued treatment or study prematurely, withdraw consent, or die before pCR in breast can be assessed, will be considered non-responders.

If a patient receives less than 80% of the protocol required treatment, undergoes surgery and achieves pCR in breast, the patient will be counted as a responder in the ITT population, but not in the evaluable population.

6.2.5. Event-free Survival and Event-free Survival at 3 Years

EFS at 3 years will be analyzed by using Kaplan Meier methods. The 95% CI for EFS at 3 years will be calculated using the log-log transformation (conftype=loglog default option in SAS PROC LIFETEST) with back transformation to a CI on the untransformed scale. The estimate of the standard error will be computed using Greenwood's formula. The analysis of EFS at 3 years will be performed in the evaluable population.

6.2.6. Overall Survival and Overall Survival at 3 Years

OS at 3 years will be analyzed by Kaplan-Meier methods. The 95% CI for OS at 3 years will be calculated using the log-log transformation (conftype=loglog default option in SAS PROC LIFETEST) with back transformation to a CI on the untransformed scale. The estimate of the standard error will be computed using Greenwood's formula. The analysis of OS at 3 years will be performed in the evaluable population and ITT population.

6.3. Quality of Life

6.3.1. Calculation of Scores for the EORTC QLQ-C30 and QLQ-BR23

The QLQ-C30 consists of 30 items (questions) grouped into 5 functional scales, 3 symptom scales, a global health status/QOL scale, and 6 single-item scales as shown in Table 2. The full questionnaire is provided in Section 9.4.

Table 2 EORTC QLQ-C30 Scales and Items

	Label	Items (Questions) Included	Possible Raw Scores of Response for Items
Global Health Status / QOL	QL2	29, 30	1-7
Functional Scales			
Physical functioning	PF2	1-5	1-4
Role functioning	RF2	6, 7	1-4
Emotional functioning	EF	21-24	1-4
Cognitive functioning	CF	20, 25	1-4
Social functioning	SF	26, 27	1-4
Symptom Scales/Items			
Fatigue	FA	10, 12, 18	1-4
Nausea and vomiting	NV	14, 15	1-4
Pain	PA	9, 19	1-4
Dyspnea	DY	8	1-4
Insomnia	SL	11	1-4
Appetite loss	AP	13	1-4
Constipation	CO	16	1-4
Diarrhea	DI	17	1-4
Financial difficulties	FI	28	1-4

The QLQ-BR23 Breast Cancer Module consists of an additional 23 questions, grouped into 2 functional scales, 3 symptom scales, and 3 single-item scales. The full QLQ-BR23 is provided in Section 9.5.

Table 3 EORTC QLQ-BR23 Scales and Items

	Label	Items (Questions) Included	Possible Raw Scores of Response for Items
Functional Scales/Items			
Body image	BRBI	39-42	1-4
Sexual functioning	BRSEF	44, 45	1-4
Sexual enjoyment	BRSEE	46	1-4
Future perspective	BRFU	43	1-4
Symptom Scales/Items			
Systemic therapy side effects	BRST	31-34, 36-38	1-4
Breast symptoms	BRBS	50-53	1-4
Arm symptoms	BRAS	47-49	1-4
Upset by hair loss	BRHL	35	1-4

Except for items 29 and 30, which form the Global Health Status/QOL scale, all other items have 4 possible scores for responses (1 = not at all, 2 = a little, 3 = quite a bit, 4 = very much). For most items, the response "very much" indicates poorer quality of life (eg, "Do you have any trouble taking a long walk?"). However, for QLQ-BR23 Module items 44, 45, and 46 regarding sexual activity, the response "very much" indicates better quality of life.

The Global Health Status/QOL items 29 and 30 ("How would you rate your overall health/quality of life during the past week?") have 7 possible scores for responses, ranging from 1 = very poor to 7 = excellent.

Raw scores for the symptom, functional, and global health status/QOL scales are calculated by taking the mean score of the items composing the scale. Raw scale scores are computed for a patient at time points for which at least half of the items composing the scale are non-missing. If less than half of the items are non-missing, the scale is considered to be missing at that time point for the patient.

Linear transformations are used to standardize the raw scores for the scales and single items, such that scores range from 0 to 100. Functional scales/items are transformed such that a higher score represents a higher ("better") level of functioning. Symptom scales/items are transformed such that a higher score represents a higher ("worse") level of symptoms. The transformations are as follows:

Functional scales / items: $S = \left\{1 - \frac{(RS-1)}{range}\right\} \times 100$

Symptom scales / items: $S = \left\{\frac{(RS-1)}{range}\right\} \times 100$

Global health status / QOL: $S = \left\{\frac{(RS-1)}{range}\right\} \times 100$

where: RS = raw score
range = maximum possible value of RS – minimum possible value of RS

Therefore, the range for single items 29 and 30 for the Global Health Status/QOL scale is 6. The range for all other single items and all other scales is 3.

The sexual functioning scale and the sexual enjoyment item from the QLQ-BR23 module use the symptom scale transformation rather than the functional scale transformation, as higher raw scores correspond to higher functioning for these items.

CCI

[redacted]

CCI [redacted]

6.3.3. Completion Analysis for EORTC QLQ-C30, EORTC QLQ-BR23, CCI and PRO-CTCAE

The number and percentage of patients who completed these instruments will be summarized, as will the reasons for non-completion of these measures. An instrument is considered completed if at least one item was answered by the patient.

6.3.4. Summary and descriptive analysis for EORTC QLQ-C30, EORTC QLQ-BR23, CCI and PRO-CTCAE

At each visit, the results from the endpoints of the above instruments (15 scales from C30, 8 scales from BR23 CCI [redacted] will be summarized using mean (and standard deviation), 95% confidence interval, and median (and range), as well as these same descriptive statistics based on change from baseline. The proportions of patients who missed expected menstrual periods from the PRO-CTCAE questionnaire will also be displayed in a similar manner.

CCI [redacted]

A graphical display corresponding to the above descriptive results will also be provided, both based on the observed values as well as based on change from baseline values.

6.3.5. Time to Definitive Deterioration in Global Health Status/Qol Per European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)

Time to definitive deterioration of patient-reported global health status/QoL will be summarized using survival analysis methods. This will include Kaplan-Meier estimate of the median and 25th and 75th percentiles, 95% CI (based on the Brookmeyer-Crowley method), Kaplan-Meier plots will also be provided. Definitive deterioration is defined as >10 points decrease from baseline without any subsequent <10 points decrease in score. Baseline is the cycle 1 day 1 visit and all visits where QLQ-C30 is completed up to and including EOT visit are considered in this analysis.

TTD (months) = [date of deterioration or censoring – enrollment date +1]/30.4375

Patients will be censored at the last time they completed an assessment if they have not deteriorated. Death will not be considered an event for TTD.

6.3.6. Time to Definitive Deterioration in Nausea and Vomiting Symptoms Per EORTC QLQ-C30

Time to definitive deterioration of patient-reported nausea and vomiting symptoms will be summarized using survival analysis methods. This will include Kaplan-Meier estimate of the median and 25th and 75th percentiles, 95% CI (based on the Brookmeyer-Crowley method), Kaplan-Meier plots will also be provided.

Items 14 and 15 in the QLQ-C30 form the nausea and vomiting symptoms scale. The raw scores are calculated by taking the mean of the two items. A linear transformation is applied as described in Section 6.3.1. Definitive deterioration is defined as >10 points decrease from baseline, cycle 1 day 1 visit, without any subsequent <10 points decrease in the linearly transformed scores at visits through the end of treatment visit.

TTD (months) = [date of deterioration or censoring – enrollment date +1]/30.4375

Patients will be censored at the last time they completed an assessment if they have not deteriorated. Death will not be considered an event for TTD.

6.3.7. Change from Baseline in Global Health Status/Qol, Functioning, and Symptoms per EORTC QLQ-C30 and EORTC QLQ BR-23[CCI]

A longitudinal mixed-effect model analyses will be used to assess change from baseline in global health status/QOL, functioning, and symptoms per EORTC QLQ-C30, EORTC QLQ BR-23[CCI]

The variables in the model will be time with baseline used as a covariate and a random effect for subject. Parameter estimates will be based on a restricted maximum likelihood method. No adjustments for multiple comparisons will be made. The baseline visit is the cycle 1 day 1 and visits though end of treatment visit will be included.

6.3.8. Change from Baseline in Proportion of Patients with Missed Expected Menstrual Period and Proportion of Patients with Deterioration in Nausea and Vomiting Symptoms

Additional patient reported outcomes will be assessed to evaluate the change from baseline in proportion of patients with missed expected menstrual period per PRO-CTCAE versus baseline.

Missed expected menstrual period will be assessed electronically using the PRO-CTCAE questionnaire, a patient-reported outcome measure developed to evaluate symptomatic toxicity in patients on cancer clinical trials.

The proportion of patients at each visit with deterioration in nausea and vomiting symptoms (vs no deterioration) will be compared based on items 14 and 15 in the QLQ-C30.

Deterioration in nausea and vomiting symptoms is defined as a ≥10 points increase from baseline for that specific time point. Improvement in nausea and vomiting symptoms is defined as a ≥10 points decrease from baseline for that specific time point. No change in nausea and vomiting symptoms would be defined as scores that do not satisfy either categories mentioned above. Baseline is the cycle 1 day 1 visit and all visits where QLQ-C30 is completed up to and including EOT visit are considered in this analysis.

6.4. **Standard Analyses**

Descriptive statistics will be used to summarize study conduct and patient disposition, baseline characteristics, and treatment administration/compliance.

- **Study Conduct and Patient Disposition** - an accounting of the study patients will be tabulated including treated, accrual by study center, assessed for AEs, laboratory data, CCI PK, etc. Patients not meeting the eligibility criteria will be identified. Patients not completing the study will be listed along with the reason for their premature discontinuation. Reasons for premature discontinuation will be summarized.

- **Demographics and Baseline Characteristics** - patient characteristics such as patient age, height, weight, BMI, gender, race, ethnicity, ECOG performance status, primary diagnosis, prior therapy (radiotherapy, surgery, systemic therapy), baseline disease site, BRCA 1 and 2 mutations, cancer histological type, prior medication, medical history, and signs and symptoms at study entry will be summarized in frequency tables, and descriptive statistics will be provided for quantitative variables.

- **Protocol Deviations** - Protocol deviations will be categorized as major or minor according to the protocol deviation specification document. Major protocol deviations that occur during the study will be summarized by deviation category for all patients in the ITT population. A by-patient listing of all major and minor deviations will be provided.

- **Treatment Administration and Compliance**

  - **Extent of Treatment**

    The extent of treatment will be summarized as follows:
    - The number and percent of patients on treatment and off for each reason
    - The number and percent of patients completing 8, 16, 24 weeks of treatment with talazoparib
    - Duration of treatment (median, minimum, maximum)
    - Cumulative dose and relative dose intensity (see Appendix 10.3 for details)

  - **Treatment Dose Modifications**

    Dosing interruption and dose modifications of study treatment will be summarized as follows including number and percent (see Appendix 10.3 for details):

- The number of patients with at least one dose reduction and the number of patients with at least one dose interruption at any time during drug administration will be reported.
- The number of patients with at least one dose reduction due to an adverse event will be reported.
- The number of patients with at least one dose interruption due to an adverse event will be reported
- Total duration (days) of dose interruptions due to adverse event will be reported
- Number of dose reductions and duration of dose reductions

- **Concomitant medications and Non-drug treatments**

  Concomitant and non-drug treatments refer to all drug and non-drug treatments taken while on active treatment (during the effective duration of study treatment), whether or not they are recorded at baseline (i.e. have stop day greater than or equal to day 1 relative to first dose of study drug). Concomitant medication will be summarized in frequency tables by treatment.

- **Follow-Up Therapy**

  Follow-up cancer therapy will be summarized as patients with particular agents as first post study therapy.

6.5. **Safety Analyses**

Safety analyses will be performed using the safety population, defined as all patients who receive any amount of study drug.

Listings of AE, SAE, death, laboratory data, vital signs, post-surgical wound examinations, and physical examinations will be provided according to reporting standard.

6.5.1. Adverse Events

Adverse events will be classified using the medical dictionary for regulatory activities (MedDRA) classification system. The severity of the toxicities will be graded according to the NCI CTCAE v.4.03 whenever possible.

Only TEAEs will be included in the adverse event summaries. Adverse events that change CTCAE grade will be reported as separate adverse events, with the start date of the event at a new grade corresponding to the stop date of the event at the previous grade. Patients with multiple occurrences of events for a given preferred term, system organ class, or overall will be counted once at the worst severity for each preferred term, system organ class, and overall, respectively. Detailed information collected for each AE will be presented in the AE listings and will include a description of the event, duration, whether the AE was serious, intensity, relationship to study drug, action taken, and clinical outcome.

Tabular summaries will present the number and percentage of patients with an event with the number of patients in the safety population as the denominator.

- Overview of TEAEs
- All TEAEs
  - By system organ class and preferred term
  - By system organ class, preferred term and maximum severity
  - By decreasing frequency of preferred term
- Study drug-related TEAEs per investigator
  - By system organ class and preferred term
  - By decreasing frequency of preferred term
  - By system organ class, preferred term, and maximum severity
- Grade 3 or 4 TEAEs
  - By system organ class and preferred term
  - By decreasing frequency of preferred term
  - Related to study drug by system organ class and preferred term
  - Related to study drug by decreasing frequency of preferred term
- TEAEs leading to study drug discontinuation
  - By system organ class and preferred term
  - By decreasing frequency of preferred term
- TEAEs associated with dose modifications (including dose reductions and dose interruptions)
  - By system organ class and preferred term
  - By decreasing frequency of preferred term
  - By system organ class, preferred term, and maximum severity
- TEAEs resulting in death
  - By system organ class and preferred term
  - By decreasing frequency of preferred term
- Serious TEAEs
  - By system organ class and preferred term
  - By decreasing frequency of preferred term
  - By system organ class, preferred term, and maximum severity
  - Related to study drug per investigator by system organ class and preferred term
  - Related to study drug per investigator by decreasing frequency of preferred term
  - With action taken of permanent discontinuation of study drug by system organ class and preferred term
  - Leading to study drug discontinuation by system organ class and preferred term

6.5.2. Laboratory abnormalities

Hematologic and chemistry laboratory data will be summarized by visit. The hematologic and chemistry laboratory results will be graded according to the NCI CTCAE v.4.03 severity grade. For parameters for which an NCI CTCAE v.4.03 scale does not exist, the frequency of patients with values below, within, and above the normal range for the local lab will be summarized. Each patient will be summarized by the worst severity grade observed for a particular laboratory parameter. This will be provided for all visits. Laboratory shift tables of baseline to maximum post-baseline result will be produced.

The number and proportion of patients with liver test elevations will be presented. Liver function test elevations will be assessed using postbaseline results for alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBL), and alkaline phosphatase (ALP) as:

- Postbaseline ALT or AST $\geq 3 \times$ ULN
- Postbaseline ALT or AST $>5 \times$ ULN
- Postbaseline AST or ALT $>10 \times$ ULN
- Postbaseline AST or ALT $>20 \times$ ULN
- TBL $> 2 \times$ ULN
- Postbaseline ALT or AST $\geq 3 \times$ ULN and TBL $> 2 \times$ ULN and ALP $< 2 \times$ ULN (at any visit)

CCI [redacted]

6.5.3. QTc Analyses

ECGs were done at screening only. The results will be listed.

6.6. Pharmacokinetic and Pharmacodynamic Analyses

The relationship between steady-state talazoparib trough concentrations with tumor response and/or safety findings after accounting for potential covariates may be evaluated. The results of any exploratory population PK/PD analysis may be reported separately from the clinical study report.

All patients treated with talazoparib for whom drug plasma results (from at least 1 visit) are available would be included in the PK analysis. Talazoparib concentration will be summarized descriptively by nominal time and talazoparib dose strength. Additionally, a subgroup of PK samples which meet pre-defined steady-state acceptance criteria will be summarized by nominal time and a within-patient average talazoparib steady-state trough concentration will be listed by patient from this population.

CCI [redacted]

CCI [redacted]

[redacted]

[redacted]

6.8. **Summary of Key Clinical Efficacy Analyses**

Type of Analysis	Endpoint	Analysis Set	Statistical Method
Primary	pCR by ICR	Evaluable Population (See 4.1.1)	Exact CI based on Blaker method (80% and 95% CI), overall and by BRCA1/BRCA2 status
Secondary	pCR by ICR	ITT Population (See 4.2)	Exact CI based on Blaker method (80% and 95% CI)
Secondary	pCR by INV	Evaluable Population (See 4.1.2)	Exact CI based on Blaker method (95% CI)
Secondary	pCR by INV	ITT Population (See 4.2)	Exact CI based on Blaker method (95% CI)
Secondary	RCB by ICR	Evaluable Population (See 4.1.1)	Exact CI based on Goodman method (95% CI)
Secondary	pCR (in breast) by ICR	Evaluable Population (See 4.1.1)	Exact CI based on Blaker method (95% CI)
Secondary	pCR (in breast) by ICR	ITT Population (See 4.2)	Exact CI based on Blaker method (95% CI)
Secondary	pCR (in breast) by INV	Evaluable Population (See 4.1.2)	Exact CI based on Blaker method (95% CI)
Secondary	pCR (in breast) by INV	ITT Population (See 4.2)	Exact CI based on Blaker method (95% CI)
Secondary	EFS at 3 years	Evaluable Population (See 4.1.1)	K-M method (median and 95% CI) 95% CI at 3 years using the log(-log) method and Greenwood's formula
Secondary	OS at 3 years	Evaluable Population (See 4.1.1)	K-M method (median and 95% CI) 95% CI at 3 years using the log(-log) method and Greenwood's formula
Secondary	OS at 3 years	ITT Population (See 4.2)	K-M method (median and 95% CI) 95% CI at 3 years using the log(-log) method and Greenwood's formula
Secondary	Time to Definitive deterioration in Global Health Status/QoL	PRO analysis population (See 7.2.2)	K-M method estimate of the median and 25th and 75th percentiles, 95% CI by Brookmeyer-Crowley method
Secondary	Time to Definitive deterioration in nausea and vomiting symptoms	PRO analysis population (See 7.2.2)	K-M method estimate of the median and 25th and 75th percentiles, 95% CI by Brookmeyer-Crowley method
Secondary	Change from baseline in Global health status/QoL, functioning, and symptoms	PRO analysis population (See 7.2.2)	Longitudinal mixed-effect model analysis
Secondary	Proportion of patients with deterioration, improvement, no change in nausea and vomiting symptoms	PRO analysis population (See 7.2.2)	Descriptive statistics
Secondary	Proportion of patients with missed expected menstrual period	PRO analysis population (See 7.2.2)	Descriptive statistics
Secondary	PK of talazoparib	PK analysis population (See 7.2.2)	Sparse sampling (through concentrations [$C_{through}$] at limited time points)

Abbreviations: ITT = intent-to-treat; pCR = pathological complete response; ICR = independent central review; RCB = residual cancer burden; EFS = event-free survival; OS = overall survival.

7. INTERIM ANALYSIS AND FINAL ANALYSES

7.1. Introduction

An interim futility analysis, designed based on Bayesian PP, is planned after 28 evaluable patients are assessed for pCR. The PP is the probability of concluding a positive result by the end of the trial based on the cumulative information in the current stage. The trial will be considered a success if the posterior probability that the true pCR rate exceeds 45% is ≥80%. Predictive probability <10% was set as the futility boundary and assumes a non-informative Beta(1,1) prior. Once 28 evaluable patients are assessed for pCR, if 11 responses or less are observed, the predictive probability of a successful trial at the full sample size is less than 10%, at which point the Sponsor would recommend stopping the study due to futility. If ≥12 responses are observed in the first 28 evaluable patients, the study will continue enrolling to 60 patients.

In the HR positive group after 6 evaluable patients have completed treatment and undergone surgery, the pCR rate will be assessed. If 2 patients achieve pCR out of the initial 6, then the posterior probability that the true pCR rate in the HR positive group is greater than 45% would be 28.9%, assuming a non- informative Beta (0.5,0.5) prior. Therefore, if 2 or more pCRs are observed, the HR positive subgroup will continue to enroll. If 1 or no pCRs are observed, then closing of the HR positive subgroup will be considered.

Interim analysis results may be used for internal business decisions regarding future study planning.

7.2. Interim Analyses and Summaries

Along with the futility analysis on pCR, the interim analysis will include outputs for demographics and baseline characteristics, treatment administration and compliance, and safety outputs for the evaluable population. The primary and secondary endpoints will be summarized, specifically pCR by INV, pCR in breast and residual cancer burden.

This study will not use a data monitoring committee.

8. REFERENCES

Blaker H. Confidence curves and improved exact confidence intervals for discrete distributions. Can J Stat. 2000 Dec;28(4):783–98.

Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics. 1982 Mar;38(1):29-41.

9. APPENDICES

9.1. Schedule of Activities

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to Study Procedures (Protocol Section 6) and Assessments (Protocol Section 7) for detailed information on each procedure and assessment required for compliance with the protocol.

Table 4. Study Schedule of Activities

Visit Identifier[a]	Screening	C1D1[b]	C1D15	C2D1	C2D15	D1 of C3-C6	End of Treament Visit[c]	Surgery	Post- surgical Follow-up[dd]	Long-Term Follow-up[d]
Visit Window	**≤28 days prior to randomization**									
Informed consent,[e] SSID number	X									
Medical history (including tumor history)	X									
Eligibility Criteria	X									
Registration	X									
Physical examination (including vital signs)[f]	X	X	X	X	X	X	X			
ECOG Performance status	X	X		X		X	X			
Baseline signs and symptoms		X								
Laboratory[g]										
Hematology	X	X	X	X	X	X	X		X	
Blood chemistry	X	X	X	X	X	X	X		X	
Urinalysis	X									
Coagulation	X								X	
CCI [redacted]		[redacted]					[redacted]			
Serum or Urine Pregnancy test/contraception check	X	X		X		X	X			
CCI [redacted]	[redacted]									

Visit Identifier[a]	Screening	C1D1[b]	C1D15	C2D1	C2D15	D1 of C3-C6	End of Treament Visit[c]	Surgery	Post- surgical Follow-up[dd]	Long-Term Follow-up[d]
Visit Window	**≤28 days prior to randomization**									
CCI [redacted]	[redacted]									
CCI [redacted]		[redacted]								
Blood sample for PK[l]				X		X (C3 and C4 only)				
CCI [redacted]		[redacted]				[redacted]	[redacted]			
CCI [redacted]		[redacted]					X			
Blood sample for BRCA status[ee]	X									
CCI [redacted]		[redacted]								
ECG[p]	X									
Radiographic Assessments[q]										
CT/PET/MRI scan CHEST[q]	X									
CT/PET/MRI scan ABDOMEN AND PELVIS[r]	X									
Bone Scan[s]	X									
Breast imaging (Mammogram/USS/MRI)[t]	X			X (USS only)		X (USS only, C4 and C6 only)				
PRO Assessments[u]										
Antiemesis medication log[v]			X	X	X	X	X		X	
EORTC QLQ-C30[w]		X	X	X	X	X	X		X	
EORTC QLQ-BR23[w]		X	X	X	X	X	X		X	
PROCTCAE[w]		X	X	X	X	X	X		X	
CCI [redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	C		[redacted]	
Tumor Tissue Specimen (FFPE)[x]								X		
Talazoparib[y]		→	→	→	→	→	→			

Visit Identifier[a]	Screening	C1D1[b]	C1D15	C2D1	C2D15	D1 of C3-C6	End of Treament Visit[c]	Surgery	Post- surgical Follow-up[dd]	Long-Term Follow-up[d]
Visit Window	**≤28 days prior to randomization**									
Concomitant medication	X	→	→	→	→	→	→	→	→	
Serious and non-serious adverse event monitoring[z]	X	→	→	→	→	→	→	→	→	
New antineoplastic therapy[aa]										X
Local recurrence/disease progression										X
Diagnosis of myelodysplastic syndrome or acute myeloid leukemia[bb]										X
Survival status[cc]										X

Abbreviations: C=Cycle; CTC=Circulating Tumor Cells; CCI CT=Computed Tomography; D=Day (of study); ECG= electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EORTC QLQ=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; FFPE=Formalin-fixed, paraffin-embedded; HRQL= health-related quality of life; HRU = healthcare resource utilization; MRI=Magnetic Resonance Imaging; PK=Pharmacokinetics; PRO=Patient reported outcomes; PROCTCAE=Patient Reported Outcomes version of the Common Terminology Criteria for Adverse Events; SSID=social security identification;USS=Ultrasound scan; CCI

a. Day relative to start of study treatment (Day 1).

b. Cycles are 4 weeks. A ± 3-day window is allowed for all study assessments, including the time between randomization and first dose. Study Day 1 is the day that the patient receives the first dose of study drug treatment. Patients must not go more than 30 days between drug dispensing visits.

c. EOT visit is usually scheduled for 28 days post last dose of study medication or after permanent treatment discontinuation or before initiation of a new antineoplastic or investigational therapy, whichever occurs first. Phone patients for adverse event follow up if they do not come to the clinic.

d. Long-term follow-up begins after safety follow-up and may be conducted by telephone every 12 weeks until the patient dies or withdraws consent for follow-up, or the study is terminated by the Sponsor.

e. Obtain any time before any study-specific procedures. Ensure consent is on the current version of the form approved by the ethics committee (EC) and Sponsor. Complete, sign, and fax or email the form with requested items to the sponsor or designee at least 2 business days before enrollment. Patient may proceed to Day 1 visit or enrollment when sponsor or designee approves by signed form or email correspondence.

f. Physical Exam: Assess systems (eg, general appearance, head, eyes, ears, nose, mouth, throat, skin, heart, lung, lymph nodes, gastrointestinal, genitourinary, neurologic, and skeletal) per standard of care at the study site or as clinically indicated by symptoms. A clinical exam of breast and axilla should be included in each physical exam. If the patient has evidence of clinical disease progression, treatment on study should be discontinued. These patients should either switch to alternate systemic therapy or go straight to surgery so as not to preclude potentially curative surgery. Vital sign measurements (blood pressure, heart rate, and temperature) and weight will also be assessed. Height will also be measured at screening.

g. Patient to complete QoL questionnaires and have blood samples collected before the first dose of study drug on Day 1. If the screening test is performed >7 days before the start of treatment, repeat the test on Day 1.

h. Anti-müllerian hormone (AMH) levels will be checked at baseline (Cycle 1 Day 1) and at the end of treatment visit to check for changes from baseline levels.

CCI [redacted]

l. Blood Sample for Pharmacokinetics: Plasma PK samples (4 mL venous blood samples collected into appropriately labeled lavender-top K_2EDTA [dipotassium ethylenediaminetetraacetic acid] tubes for talazoparib determination) will be collected pre-dose on C2D1, C3D1, and C4D1 only. Patients must be instructed to withhold their daily dose of talazoparib on PK sampling days until the pre-dose PK sample and safety assessments (ie, hematology, blood chemistry, and ECGs) have been completed. All patients: Record the dose amounts and time of dose administration on both the day of and the day before PK sampling. Record the date and time of each PK sample. For additional details, see Protocol Section 7.5 and the Study Laboratory Manual.

CCI [redacted]

p. Single ECG, to be done locally.

q. If scans are done within 6 weeks prior to the start of the screening period (informed consent from signing date), they do not need to be repeated. Any of the imaging modalities (CT/PET/MRI) can be used.

r. Pelvis scan (CT/PET/MRI) to be done as clinically indicated.

s. Bone scan to be done as clinically indicated.

t. Breast imaging (Mammogram/USS/MRI): any one of the three imaging modalities can be used; unless indicated otherwise in the Schedule of Activities. USS have a window of ±3 days.

u. Ask the patient to complete the questionnaires before any other study activities. Questionnaires should be completed while alone in the same order at each visit.

v. An electronic patient reported-antiemesis medication log will be used to record antiemesis medication taken by the patients for 7 consecutive days prior to each clinical visit. Since there is no patient visit scheduled for Day 7, the patient will be asked to record this information at home.

w. Patient reported outcomes will be assessed electronically to evaluate global health status/QoL, functions, and symptoms using the EORTC QLQ C30 and QLQ BR23 questionnaires; CCI [redacted] Additional patient reported outcomes will be assessed electronically to evaluate the proportion of patients with missed expected menstrual period per PRO-CTCAE.

x. Tumor tissue from the surgical specimen will be required. This should be sent to the central lab as soon as possible for evaluation of the primary endpoint (pathological complete response).

y. Drug supply must be taken into account when scheduling visits during windows. Visit procedures may be split across the window to allow for drug resupply and completion of study procedures. Instruct patient to self-administer study drug treatments. Administer talazoparib in the clinic on study days with PK assessments.

z. Collect serious and non-serious adverse event information from the time of signed informed consent through and including a minimum of 28 calendar days after the last administration of the IP. If a patient begins a new anticancer therapy, the recording period for non-serious AEs ends at the time the new treatment is started.

aa. Record subsequent treatment information for patients starting a new antineoplastic or investigational therapy.

bb. Record any diagnosis of myelodysplastic syndrome or acute myeloid leukemia and report as a serious adverse event (SAE). Provide tissue samples and other supporting data used to enable the diagnosis of myelodysplastic syndrome or acute myeloid leukemia for central review if requested.

cc. Obtain survival status every 12 weeks by any means including telephone, clinic visit, chart review, or by communicating with an individual (eg family, friend, referring health care provider) who is knowledgeable of the patient's survival status.

dd. Post-surgical follow-up: a clinical examination of the post-surgical wound should be carried out and laboratory tests as indicated should be performed.

ee. BRCA testing can be performed using a local, CLIA certified blood test. If local test is done (other than Myriad BRACAnalysisCDx post 2016), an additional sample will need to be sent for central testing to MYRIAD genetics. Patients must also consent to a blood sample for central genomic assessment using the BRACAnalysisCDx test by Myriad Genetics, except for patients who already have evidence of BRCA1/2 mutation by MYRIAD BRCAnalysisCDx post 2016. Blood samples for central BRCA status: collect two 10 mL samples of blood into appropriately labeled tubes at screening; send to Myriad Genetics for analysis. See Central Laboratory Manual and sample collection instructions contained in the provided kit. If positive gBRCA 1/2 status has been confirmed by local test, patients may enroll and commence study treatment, provided all other inclusion/exclusion criteria are met and screening tests have been satisfactorily completed. In the event of discrepant results, where the local test is positive for gBRCA1/2 mutation and the central Myriad BRACAnalysis test is negative, the decision on further continuation on trial will be decided by the investigator based on a risk-benefit evaluation.

9.2. **Data Derivation Details**

Enrollment/Randomization	Date of assignment of the randomization number
Study Day 1	1st Dose date
Study Day (At/Post 1st dose date)	Assessment Date – 1st Dose Date +1
Study Day (Prior 1st dose date)	Assessment Date – 1st dose date
Study start	Day 1 of Cycle 1
Day 1 (cycle start date) of Cycle x	Day 1 of a cycle is every 28 days.
Cycle length (all but final cycle)	Cycle length is 28 days.
Final cycle	For patients off treatment, from Day 1 of final cycle to 28 days after final dose or until start of new anticancer treatment (whichever comes first). For patients on treatment, from Day 1 of most recent cycle start to protocol specified cycle length.
Follow-up Period for AEs	From 28 days after final dose until start of new anticancer treatment (whichever comes first).
Baseline lab values	From date closest to, but prior to, start of study treatment.
Baseline triplicate ECGs	Cycle 1 Day 1 dose or from date closest to, but prior to, start of study treatment if C1D1 is not available.
Tumor assessment baseline values	From date closest but prior to first dose.
Adequate baseline tumor assessment	Within 28 days prior to first dose. Maximum diameter reported for each target lesion listed. All required pre-treatment scans done.

9.3. **Study Treatment Modification and Compliance**

9.3.1. Dose Modification

Daily dosing of talazoparib can be interrupted for recovery from toxicity for up to 28 days. Thereafter, treatment at the same or a reduced dose can be considered. Dose modifications should be made based on observed toxicity as described in Protocol Section 5.4.

The daily dose of talazoparib may be reduced sequentially in 0.25 mg per day increments depending on the degree of toxicity.

9.3.2. Summarizing Relative Dose Intensity (RDI)

Talazoparib is administered orally once a day for every 4-week cycle for 24 weeks. All patients will receive a starting dose of 1 mg/day of talazoparib, with the exception of patients with baseline moderate renal impairment who will receive a starting dose of 0.75 mg/day of talazoparib.
The denominator for tables summarizing dosing will be all patients who receive at least one dose of talazoparib.

Overall RDI of talazoparib will be calculated as follows:

- patient starting the study at 1 mg/day
  Overall RDI (%) = 100 × [overall cumulative dose] / 168

- For the patient starting the study at 0.75 mg/day
  Overall RDI (%) = 100 × [overall cumulative dose] / 126 (corresponding to 0.75 × 168)

9.4. **European Organisation for Research and Treatment of Cancer Quality of Life Instrument (EORTC-QLQ-C30)**

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

Please fill in your initials:

Your birthdate (Day, Month, Year):

Today's date (Day, Month, Year):

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

During the past week:		**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go to the next page

During the past week:		**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17.	Have you had diarrhea?	1	2	3	4

18.	Were you tired?	1	2	3	4
19.	Did pain interfere with your daily activities?	1	2	3	4
20.	Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21.	Did you feel tense?	1	2	3	4
22.	Did you worry?	1	2	3	4
23.	Did you feel irritable?	1	2	3	4
24.	Did you feel depressed?	1	2	3	4
25.	Have you had difficulty remembering things?	1	2	3	4
26.	Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27.	Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28	Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

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

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

1	2	3	4	5	6	7
Very Poor						Excellent

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

1	2	3	4	5	6	7
Very Poor						Excellent

9.5. European Organisation for Research and Treatment of Cancer Quality-of-Life Breast Cancer Module QLQ-BR23

EORTC QLQ - BR23

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

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Did you have a dry mouth?	1	2	3	4
32. Did food and drink taste different than usual?	1	2	3	4
33. Were your eyes painful, irritated or watery?	1	2	3	4
34. Have you lost any hair?	1	2	3	4
35. Answer this question only if you had any hair loss: Were you upset by the loss of your hair?	1	2	3	4
36. Did you feel ill or unwell?	1	2	3	4
37. Did you have hot flushes?	1	2	3	4
38. Did you have headaches?	1	2	3	4
39. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
40. Have you been feeling less feminine as a result of your disease or treatment?	1	2	3	4
41. Did you find it difficult to look at yourself naked?	1	2	3	4
42. Have you been dissatisfied with your body?	1	2	3	4
43. Were you worried about your health in the future?	1	2	3	4

During the past four weeks:	Not at All	A Little	Quite a Bit	Very Much
44. To what extent were you interested in sex?	1	2	3	4
45. To what extent were you sexually active? (with or without intercourse)	1	2	3	4
46. Answer this question only if you have been sexually active: To what extent was sex enjoyable for you?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
47. Did you have any pain in your arm or shoulder?	1	2	3	4
48. Did you have a swollen arm or hand?	1	2	3	4
49. Was it difficult to raise your arm or to move it sideways?	1	2	3	4
50. Have you had any pain in the area of your affected breast?	1	2	3	4
51. Was the area of your affected breast swollen?	1	2	3	4
52. Was the area of your affected breast oversensitive?	1	2	3	4
53. Have you had skin problems on or in the area of your affected breast (e.g., itchy, dry, flaky)?	1	2	3	4

CCI

[redacted]

CCI

[redacted]

9.7. Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events

58. **PRO-CTCAE™ Symptom Term:** Missed expected menstrual period		
In the last 7 days, did you MISS AN EXPECTED MENSTRUAL PERIOD?		
O Yes	O No	O Not applicable

9.8. List of Abbreviation

Abbreviation	Term
AE	Adverse Event
ALT	Alanine Aminotransfersae
CCI [redacted]	[redacted]
ANC	Absolute neutrophil count
AST	Aspartate Aminotransfersae
BC	Breast Cancer
BRCA	Breast cancer susceptibility gene
BRCA1	Breast cancer susceptibility gene 1
BRCA2	Breast cancer susceptibility gene 2
BUN	Blood Urea Nitrogen
CI	Confidence Interval
CR	Complete Response
CRF	Case Report Form
CSA	Clinical Study Agreement
CT	Computed Tomography
CTA	Clinical Trial Application
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CCI [redacted]	[redacted]
CxDy	Cycle x, Day y (refer to Section 9.1. Schedule of Activities)
DCIS	Ductal in Situ Carcinoma
DNA	Deoxyribonucleic Acid
DU	Dispensable Unit
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free Survival
EORTC	European Organization for Research and Treatment of Cancer
CCI [redacted]	[redacted]
ER	Estrogen Receptor
EU	European Union
FDA	Food and Drug Administration
FU	Follow Up

gBRCA	Germline mutation Breast cancer susceptibility gene
Hb	Hemoglobin
HER2	Human Epidermal Growth Factor Receptor 2
IB	Investigator's Brochure
ICR	Independent Central Review
ID	Identification
INR	International Normalized Ratio
INV	Investigator assessment
ITT	Intent to Treat
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
N/A	Not Applicable
NCI	National Cancer Institute
OS	Overall Survival
pCR	Pathological Complete Response
PK	Pharmacokinetic
PRO	Patient-Reported Outcome
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
QD	once daily
QLQ	Quality of Life Questionnaire
QoL	Quality of Life
QT_c	QT interval corrected for heart rate
RCB	Residual Cancer Burden
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease or Standard Deviation (depending on context)
TNBC	Triple-negative Breast Cancer
ULN	Upper Limit of Normal
v	version
WBC	White Blood Cells