Medivation, Inc.

STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 3, Open-Label, Randomized, Parallel, 2-Arm, Multi-Center Study of Talazoparib (BMN 673) versus Physician's Choice in Germline BRCA Mutation Subjects with Locally Advanced and/or Metastatic Breast Cancer, Who Have Received Prior Chemotherapy Regimens for Metastatic Disease
Protocol Identifier:	673-301; C3441009
Phase	3
Investigational Product:	Talazoparib (also known as MDV3800, BMN 673)
Indication:	Locally advanced and/or metastatic breast cancer with germline BRCA1 or BRCA2 mutations
Sponsor:	Medivation, Inc., a wholly owned subsidiary of Pfizer Inc. 525 Market Street, 36th Floor San Francisco, CA 94105 PPD
IND and EudraCT Numbers:	108708 and 2013-002716-28
Preparer:	
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Protocol: 673-301; B3441009

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ATC	Anatomical therapeutic chemical
BOR	Best objective response
CBR24	Clinical benefit rate at 24 weeks
CI	Confidence interval
CNS	Central nervous system
CR	Complete response
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EORTC	European Organization for Research and Treatment of Cancer
HR	Hazard ratio
ITT	Intent-to-treat
IRF	Independent radiology facility
IXRS	Interactive voice/ web response system
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetics
PR	Partial response
PRO	Patient reported outcome
QLQ-BR23	EORTC Quality of Life Questionnaire - Breast Cancer Module
QLQ-C30	EORTC Quality of Life Questionnaire
QOL	Quality of Life
RECIST v1.1	Response Evaluation Criteria in Solid Tumors version 1.1
SAP	Statistical analysis plan
SMQ	Standardized MedDRA Query
TEAE	Treatment-emergent adverse event

1 INTRODUCTION

This statistical analysis plan (SAP) contains definitions of analysis populations and endpoints, outlines the timing of statistical analyses, and provides a comprehensive description of statistical analyses to be implemented to assess the clinical efficacy and safety of protocol 673-301: A Phase 3, Open-Label, Randomized, Parallel, 2-Arm, Multi-Center Study of Talazoparib (BMN 673) versus Physician's Choice in Germline BRCA Mutation Subjects with Locally Advanced and/or Metastatic Breast Cancer, Who Have Received Prior Chemotherapy Regimens for Metastatic Disease.

2 STUDY OVERVIEW

The study is a phase 3, open-label, 2:1 randomized, 2-arm study of talazoparib versus protocol-specified physician's choice of treatment. Patients with germline BRCA mutations with locally advanced or metastatic breast cancer who have received no more than 3 prior cytotoxic chemotherapy regimens for locally advanced and/or metastatic breast cancer will be enrolled.

Options for physician's choice include 1 of the following single-agent chemotherapies: capecitabine, eribulin, gemcitabine, or vinorelbine. The physician's choice of treatment must be determined prior to randomization.

Patients will be assigned to 1 of 2 study treatment groups via randomization in a 2:1 ratio (talazoparib:physician's choice) using the following stratification factors:

- Number of prior cytotoxic chemotherapy regimens for locally advanced and/or metastatic disease (0 vs 1, 2, or 3)
- Triple-negative (estrogen-receptor negative, progesterone-receptor negative, human epidermal growth factor receptor 2 [HER2]-negative) vs non triple-negative receptor status based on most recent biopsy
- History of central nervous system (CNS) metastasis vs no CNS metastasis

Treatment with talazoparib or physician's choice will continue until radiographic disease progression as determined by the central independent radiology facility (IRF) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1; Eisenhauer et al, 2009) as described in the protocol, unacceptable toxicity, consent withdrawal, physician's decision to terminate treatment, or sponsor's decision to terminate the study. While study treatment is open-label, steps will be taken to ensure designated sponsor staff responsible for study conduct and IRF members are appropriately blinded to patient treatment identity throughout the study per the Data Handling Plan and IRF charter.

Tumor assessments (computed tomography [CT] scans, magnetic resonance imaging (MRI), or x-ray) will be performed every 6 weeks from the date of randomization for the initial 30 weeks, and every 9 weeks thereafter. If bone metastasis is present at screening/baseline, a bone scan will be repeated every 12 weeks and as clinically indicated. Patients who

discontinue from study drug for any reason other than radiographic disease progression or initiation of a new antineoplastic therapy must continue imaging assessments until radiographic progression as determined by the IRF, unless the patient withdraws consent. Follow-up for survival status and anticancer treatment will continue until death.

Safety will be assessed by evaluation of adverse events, clinical laboratory tests, vital signs, and physical examination findings throughout the study. An independent Data Monitoring Committee (DMC) will monitor safety during the study on a regular basis. The committee will operate independently from the sponsor and the investigators as described in the DMC charter.

Quality of life (QOL) will be assessed using questionnaires.

For the talazoparib group, pharmacokinetics (PK) will be assessed by blood sample collection for determination of plasma talazoparib exposure.

3 STUDY OBJECTIVES

The primary objective of the study is to compare progression-free survival (PFS) of patients treated with talazoparib as a monotherapy relative to those treated with protocol-specified physician's choice.

The primary analysis of PFS will be based on radiographic progression events as determined by the central IRF per RECIST v1.1 and deaths due to any cause.

The secondary objectives of the study are to evaluate:

- Objective response rate (ORR)
- Overall survival (OS)
- Safety
- PK of talazoparib

The exploratory objectives are to evaluate:

- Duration of response (DOR)
- QOL (European Organization for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaire [QLQ-C30] / EORTC Quality of Life Questionnaire – Breast Cancer Module [QLQ-BR23])
- Research assessments related to blood and tumor sampling that includes characterization of tumor sensitivity and resistance to talazoparib

4 STUDY ENDPOINTS

Primary Endpoint:

- Radiographic PFS

Secondary Endpoints:

- ORR
- OS
- Safety
  - The incidence of adverse events, including serious adverse events
  - Change in clinical laboratory tests (serum chemistry and hematology)
  - Change in vital signs
  - Concomitant medication use
- PK of talazoparib

Exploratory Endpoints:

- DOR
- EORTC QLQ-C30/EORTC QLQ-BR23 QOL measures
- Research assessments related to blood and tumor sampling that includes characterization of tumor sensitivity and resistance to talazoparib

5 SAMPLE SIZE CONSIDERATIONS

This study is designed with adequate power to detect certain effect sizes for the PFS and OS endpoints.

For PFS, based on a 2:1 randomization allocation ratio (talazoparib:physician's choice), a total of 288 PFS events will provide 90% power for a 2-sided log-rank test at a 0.05 significance level to detect a hazard ratio [HR] = 0.67. Assuming an exponential distribution of PFS, this corresponds to an increase in median PFS from 4.6 months in control arm to 6.9 months in active arm (from 20 to 30 weeks; a 50% increase in median PFS). With the current design, the minimum observed effect that would result in statistical significance for PFS is a 28% improvement in median PFS (HR = 0.78), from 4.6 to 5.9 months (from 20 to 25.6 weeks).

Up to 429 patients will be randomly assigned to 1 of 2 treatment groups (talazoparib or physician's choice) in a 2:1 ratio and followed to observe the targeted number of 288 PFS events.

For OS, approximately 321 death events will provide 80% power for a 2-sided log-rank test at an overall 0.05 significance level to detect a HR = 0.72. Assuming an exponential distribution of OS, this corresponds to an increase in median OS from 20 months in control arm to 27.8 months in active arm.

6 ANALYSIS POPULATIONS

6.1 Intent-to-Treat Population

The intent-to-treat (ITT) analysis population is defined as all randomized patients. The ITT population will be analyzed according to the treatment assigned at randomization (not by actual treatment received).

6.2 ITT with Measurable Disease Population

The ITT with measurable disease analysis population is defined as all patients in the ITT population who have at least 1 target lesion identified at baseline.

For analyses using IRF assessment, patients will be included in the measurable disease population if at least 1 IRF reader identified at least 1 target lesion at baseline.

For analyses using investigator assessment, patients will be included in the measurable disease population if the investigator identified at least 1 target lesion at baseline.

6.3 Safety Population

The safety analysis population is defined as all patients who receive any study drug (talazoparib or protocol-specified physician's choice). The safety population will be analyzed according to the actual treatment received (not by treatment assigned).

6.4 Pharmacokinetics Population

The PK analysis population is defined as all patients who receive at least 1 dose of talazoparib and provide at least 1 evaluable PK assessment.

6.5 PRO-Evaluable Population

The PRO-Evaluable Population is defined as all patients who have completed the PRO questionnaire at baseline and at least one visit post baseline.

7 DEFINITIONS, COMPUTATIONS, AND CONVENTIONS

The statistical principles applied in the design and planned analyses of this study are consistent with International Council for Harmonisation (ICH) E9 guidelines (ICH 1998) and Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2007).

All statistical analyses detailed in this SAP will be conducted using SAS version 9.1.3 or higher.

7.1 Definitions

Study day for efficacy: Study day for efficacy will be calculated in reference to the date of randomization (study day 1). For assessments conducted on or after the randomization date, study day is calculated as (assessment date – randomization date + 1). For assessments conducted before the randomization date, study day is calculated as (assessment date – randomization date). There is no study day 0.

Study day for safety: Study day for safety will be calculated in reference to the date of the first dose of study drug. For assessments conducted on or after the date of the first dose of study drug, study day will be calculated as (assessment date – date of first dose of study drug + 1). For assessments conducted before the date of the first dose of study drug, study day is calculated as (assessment date – date of first dose of study drug). There is no study day 0.

Treatment-emergent period: The treatment-emergent period is defined as the period of time from the date and time of the first dose of study drug through 30 days after the last dose (permanent discontinuation of study drug) or the day before initiation of a new antineoplastic therapy, whichever occurs first. The treatment-emergent period will be used in the summaries of treatment-emergent adverse events (TEAEs).

Baseline and postbaseline value: Unless otherwise specified, a baseline value is defined as the last assessment on or before the date of randomization, including tumor assessment, QOL and baseline characteristics. A postbaseline value is defined as an assessment obtained after the randomization date.

Baseline and postbaseline value for safety analyses: Unless otherwise specified, a baseline value for safety analyses is defined as the last value before the date/time of first dose of study drug for laboratory tests, vital sign assessments, and electrocardiogram (ECG) data.
A postbaseline value for safety analyses is defined as a measurement taken after the date/time of first dose of study drug. If multiple values are present for the same date, the average of these values will be used in the summaries by visit, and the worst toxicity grade will be used in the summaries of toxicity grade by laboratory tests.

Last dose date: Date of the last dose (actual dose > 0 mg) from the drug administration electronic case report form (eCRF).

7.2 Reporting Conventions

Unless otherwise specified, the following conventions will be applied to all analyses:

- Mean and median values will be formatted to 1 more decimal place than the measured value. Standard deviation values will be formatted to 2 more decimal places than the measured value; minimum and maximum values will be presented to the same number of decimal places as the measured value.
- Percentages will be rounded to 1 decimal place. Number and percentage values will be presented as xx (xx.x%).

- Listings will be sorted for presentation in order of treatment group, patient identifier (ID), and date of procedure or event.
- Analysis and summary tables will have the analysis population sample size (ie, number of patients).
- Laboratory data will be reported using standard international (SI) units; as local laboratories are used for this study, conversion factors from conventional units will be listed in the clinical study report.
- 1 inch = 2.54 cm.
- Time-to-event or duration of event endpoints will be based on the actual date the radiograph was obtained rather than the associated visit date.
- Hazard ratios and odds ratios will be rounded to 2 decimal places.
- For by-visit observed data analyses, percentages will be calculated based on the number of patients with nonmissing data as the denominator unless otherwise specified.
- For time-to-event right-censored data, the summary statistics and descriptions will include Kaplan-Meier plots and/or life tables.
- For other continuous endpoints, the summary statistics will include mean, standard deviation, median, and range (minimum and maximum).
- For categorical endpoints, the summary statistics will include frequency counts and percentages.
- Confidence intervals (CIs), when presented, will generally be constructed at the 95% level. For binomial variables, exact methods will be employed unless otherwise specified.
- P-values will be rounded to 4 decimal places. P-values that round to 0.0000 will be presented as '< 0.0001' and p-values that round to 1.000 will be presented as '> 0.9999'.
- Medical history and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA v 18.0). Adverse event severity will be evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE v.4.03).
- Prior therapies and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary and summarized by Anatomical Therapeutic Chemical (ATC) medication class and preferred names.

7.3 Conventions for Dates

Conventions for calculations with dates are as follows:

- Dates will be stored as numeric variables in the SAS analysis files and reported in DDMMMYYYY format (ie, the Date9. datetime format in SAS).
- Dates recorded in comment fields will not be imputed or reported in any specific format.

- Age will be calculated in years as integer part of (RANDOMIZATION DATE - DATE of BIRTH + 1)/365.25. If both day and month fields are missing, impute missing day and month as July 1st. If the year field is missing, age will be set as missing.
- Intervals that are presented in weeks will be transformed from days to weeks by using the following conversion formula, and rounding to 1 decimal place:

  WEEKS = DAYS / 7
- Intervals that are presented in months will be transformed from days to months by using the following conversion formula, and rounding to 1 decimal place:

  MONTHS = DAYS / 30.4375

Detailed rules for imputation of missing/partially missing dates for adverse events, prior/concomitant medications/procedures, and breast cancer diagnosis are provided in Appendix 1.

7.4 Pooling of Data from Sites with Small Enrollment

The analyses will not be stratified by study site and the primary analyses of endpoints will not be adjusted by study site or pooling of study sites. No data-pooling rules are specified for this study.

7.5 Treatment Group Presentation

Patient disposition, protocol deviations, demographics and baseline characteristics, medical history, prior medications and procedures, and efficacy data summaries will be presented by randomized treatment group (talazoparib vs overall physician's choice [includes capecitabine, eribulin, gemcitabine, and vinorelbine]). Unless otherwise specified, safety data summaries will be presented by the treatment actually received (talazoparib, capecitabine, eribulin, gemcitabine, vinorelbine, and overall physician's choice). Safety subgroup analyses will be presented by talazoparib versus overall physician's choice.

7.6 Handling Missing Data

Missing data will not be imputed unless otherwise specified elsewhere in the SAP. Details regarding handling of missing QOL data are provided in Section 9.8.5.3.1. Missing dates or partially missing dates will be imputed conservatively for adverse events and prior/concomitant medications/procedures. Specific rules for handling of missing or partially missing dates for date of birth, adverse events, prior/concomitant medications/procedures, and diagnosis of breast cancer are provided in Section 7.3 and Appendix 1.

7.7 Visit Windows

Visit windows for safety and QOL time points are defined in Appendix 5.

8 TIMING OF ANALYSES

The analysis of PFS, the primary endpoint, will be conducted when approximately 288 PFS events by IRF occur in the 2 treatment groups. At that time, approximately 160 deaths are expected. If the 2-sided hypothesis test of PFS is statistically significant at a 0.05 significance level, the interim analysis of OS will be performed at a 0.0001 significance level at the time of the PFS analysis. OS data will be summarized descriptively with the HR and its 95% CIs presented for each treatment group.

The final analysis of OS will be conducted when approximately 321 death events occur as described in Section 9.8.3.2. Details regarding the multiplicity adjustment of the efficacy analyses are provided in Section 9.8.1.

9 STATISTICAL METHODS

9.1 Patient Disposition

Patient populations will be summarized by treatment group for all patients randomized and will include the number and percentage of patients in the ITT, safety, ITT with measurable disease, and PK populations.

The number and percentage of patients who discontinue study drug and the reasons for discontinuation will be summarized by treatment group for all patients in the ITT population.

Patient disposition will be summarized by treatment group for all patients in the ITT population. This will include number and percentage of patients still on active treatment, in long-term follow-up, and discontinued from the study. Reasons for study discontinuation will be summarized.

9.2 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 by treatment group as randomized. A by-patient listing of all major and minor deviations will be provided.

Patient eligibility including inclusion and exclusion criteria that were not met at randomization will be summarized for all patients in the ITT population.

9.3 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment group as randomized for all patients in the ITT population and as actual treatment received for all patients in safety population. The summary of demographic and baseline characteristics will include:

- Age (continuous and categorical variable: < 50, 50 to < 65, ≥ 65), sex, ethnicity, race, weight, and body mass index (BMI)
- Geographic region: North America (United States), Europe (Belgium, France, Germany, Ireland, Italy, Poland, Spain, United Kingdom, Russia, Ukraine, Israel), and rest of the world (Brazil, Korea, Australia, Taiwan)
- Eastern Cooperative Oncology Group (ECOG) performance status

9.4 Disease Characteristics and Prior Breast Cancer Therapies

The following baseline disease characteristics will be summarized by treatment group as randomized for all patients in the ITT population.

- Tumor type (ductal, lobular, other, unknown)
- Receptor status on most recent pathology results [(triple-negative, estrogen receptor-positive (ER^+), progesterone receptor-positive (PR^+), or $HER2^+$]
- BRCA status (BRCA1 or BRCA2) as determined by the central laboratory or by a Medivation-approved local laboratory genetic test
- Time (years) from initial diagnosis of breast cancer to randomization
- Time (years) from initial diagnosis of advanced breast cancer to randomization
- Time (years) from the start date of first cytotoxic therapy for advanced breast cancer to randomization
- Time (years) from the start date of first antineoplastic therapy for advanced breast cancer to randomization
- Time (years) from initial diagnosis of breast cancer to initial diagnosis of advanced breast cancer
- Number of patients with measurable disease as assessed by IRF and investigator
- Number of patients with non-measurable disease as assessed by IRF and investigator
- Number of metastatic sites as assessed by IRF and investigator (1,2, 3+)
- Location of metastatic disease sites as assessed by IRF and investigator
- Number of patients with bone-only metastatic disease as assessed by IRF and investigator
- Number of patients with visceral disease as assessed by IRF and investigator

Stratification factors as assigned by the interactive voice/web response system (IXRS) and as derived from eCRFs will be presented side-by-side within each treatment group as follows:

- Number of prior cytotoxic chemotherapy regimens for locally advanced and/or metastatic disease (0 vs > 0; Prior Study Cancer Treatment eCRF)
- Triple-negative disease (yes vs no; Pathology of Breast Cancer eCRF)
- History of CNS metastasis status (yes vs no; Brain Scan eCRF)

Prior breast cancer treatments will be summarized by treatment group as randomized for all patients in the ITT population as follows:

- Number of prior cytotoxic chemotherapy regimens for locally advanced and/or metastatic disease (0, 1, 2, or 3)
- Number of patients who received the following prior therapies:
  - Antineoplastic therapy
  - Hormonal/aromatase inhibitor treatment
  - Neoadjuvant/adjuvant therapy
  - Radiotherapy
  - Anthracycline treatment
  - Taxane treatment
  - Capecitabine treatment
  - Eribulin treatment
  - Platinum treatment as neoadjuvant/adjuvant therapy
  - Platinum treatment for locally advanced or metastatic disease
  - Immunotherapy
  - CDK4/6 inhibitors

Prior antineoplastic therapies will be summarized by ATC medication class and preferred names. In addition, prior antineoplastic therapies will be separately summarized by ATC medication class and WHO Drug Name. This will permit the proprietary and generic drugs to be combined as a single medication (eg eribulin and eribulin mesylate).

9.5 Medical History

General medical history and oncology history will be summarized by body system and by treatment group as randomized for all patients in the ITT population.

9.6 Concomitant Medications and Subsequent Therapies

Concomitant medications will be summarized by treatment group as actual treatment received for all patients in the safety population. Medications are considered concomitant if exposure occurs during the treatment-emergent period.

Antineoplastic therapies initiated postbaseline will be summarized by treatment group as randomized for all patients in the ITT population.

A patient reporting use of the same medication more than once will be counted once in the calculation of the number and percentage of patients who received that medication.

9.7 Extent of Exposure and Study Drug Compliance

Study drug exposure and relative dose intensity will be calculated based on drug administration eCRFs. Summary statistics will be presented by treatment group as actual treatment received for all patients in the safety population as follows:

- Duration of exposure to study drug (months): Definition is presented in Table 1 for talazoparib as well as each of the 4 physician's choice therapies. For patients who are continuing study drug at the data cutoff date, the data cutoff date will be used as date of last dose of study drug.
- Duration of treatment by time period.
- Relative dose intensity (%): Relative dose intensity will be calculated as actual dose intensity divided by planned dose intensity (Table 1).

Table 1: Dose Intensity Derivation

Study Drug	Duration of Exposure (months)	Actual Dose Intensity	Planned Dose Intensity
Talazoparib	(Last dose date – First dose date +1)/ 30.4375	Cumulative actual dose received divided by (last dose date – first dose date +1)	1 mg/day
Capecitabine	(Last dose date –First dose date + 8)/ 30.4375	Cumulative actual dose received divided by (last dose date – first dose date + 8)	Planned dose at cycle 1 day 1 × 14 divided by 21
Vinorelbine	(Last dose date –First dose date + 7)/ 30.4375	Cumulative actual dose received divided by (last dose date – first dose date + 7)	Planned dose at cycle 1 day 1 × 3 divided by 21
Eribulin and gemcitabine	(Last dose date –First dose date + 14)/ 30.4375	Cumulative actual dose received divided by (last dose date – first dose date + 14)	Planned dose at cycle 1 day 1 × 2 divided by 21

Dose modifications will be summarized as follows:

- Number of patients with at least 1 dose reduction due to adverse event
- Number of dose reductions due to adverse event (1, 2, 3, > 3)
- Number of patients with at least 1 dose interruption due to adverse event for talazoparib and capecitabine treatment groups
- Number of dose interruptions due to adverse event (1, 2, 3, > 3) for talazoparib and capecitabine treatment groups
- Duration (days) of dose interruptions due to adverse event for each dose interruption for talazoparib and capecitabine treatment groups
- Total duration (days) of dose interruptions due to adverse event for each patient in the talazoparib and capecitabine treatment groups
- Time to 1st dose reduction for treatment with talazoparib.

For patients treated with capecitabine, a delay in starting a new 3-week cycle will be considered a dose interruption.

9.8 Efficacy Analyses

The primary efficacy measure will be the ability of the treatment to delay the time to progression of breast cancer, evaluated using sequential imaging assessments digitally submitted to, and reviewed by the IRF. Radiographic response or progression will be determined by IRF assessment of CT, MRI, x-ray, and bone scans according to RECIST v1.1. A complete description of RECIST v1.1 is provided in protocol Section 24.3. The secondary efficacy measures include ORR and OS.

Only tumor assessments and deaths that occur on or before the data cutoff date will be included in analyses.

Stratified analyses will use the same stratification factors that were used to stratify the randomization schedule as documented in the IXRS. The stratification factors include the following:

- Number of prior cytotoxic chemotherapies for locally advanced and/or metastatic breast cancer (0 vs 1, 2, 3)
- Triple-negative receptor status (yes vs no)
- History of central nervous system metastasis (yes vs no)

If the overall stratification error rate is ≥ 10%, a sensitivity analysis will be performed using the actual stratification factors as documented in the clinical database for the primary and secondary efficacy endpoints. If the model does not converge because 1 stratum has too few patients, the stratification factor with too few patients in 1 stratum will not be included in the stratified analysis.

9.8.1 Multiplicity Adjustment for Efficacy Analyses

To maintain the overall 2-sided type I error rate at 0.05, the primary and secondary efficacy analyses will be protected under a multiplicity adjustment schema using gate-keeping methodology. The details of the 3-step testing approach are as follows:

Step 1: Compare PFS for talazoparib versus physician's choice when approximately 288 PFS events by IRF occur. Compute the p-value for the PFS comparison. If the p-value is < 0.05 and the HR ($\lambda_{talazoparib}/\ \lambda_{physician's\ choice}$) is < 1, declare statistical significance for PFS with talazoparib versus physician's choice and proceed to step 2. If the statistical significance for PFS cannot be declared, the formal hypothesis tests for OS will not be performed.

Step 2: At the time of the PFS analysis (targeted 288 PFS events), compare OS for talazoparib versus physician's choice as follows:

- Conduct an interim analysis of OS at a 0.0001 significance level using Haybittle-Peto boundary (Haybittle, 1971; Peto et al, 1976). Descriptive summaries including the HR and its 95% CIs will be presented for each treatment group. No formal hypothesis testing will be performed for interim OS. Final OS analysis will be performed in Step 3.

Step 3: At the final analysis of OS (targeted 321 death events), compare OS for talazoparib versus physician's choice as follows:

- If the result of the test specified in step 1 is statistically significant, conduct the OS analysis at a 2-sided 0.0499 significance level. If the p-value of the OS test is < 0.0499 and the HR ($\lambda_{talazoparib}/ \lambda_{physician's\ choice}$) is < 1, declare superiority of treatment with talazoparib for OS.

No adjustments are planned for multiple testing/comparisons in the secondary and exploratory hypothesis tests except OS.

9.8.2 Primary Efficacy Endpoint

The primary efficacy endpoint is PFS. The analysis of PFS is event-based and will be conducted using the ITT population after approximately 288 PFS events by IRF occur. PFS analysis will include all data through the date when approximately 288 PFS events occur.

The recorded PFS date is defined as the date of the earliest tumor assessment visit at which progression is declared or the date of death due to any cause without progression. Only tumor assessments determined as "adequate" (not in the "not evaluable" category) by the IRF will be considered in the determination of progression and censoring dates for the primary analysis of PFS.

9.8.2.1 Primary Analysis

PFS for the primary analysis is defined as time from randomization until the date of radiologic progressive disease per RECIST v1.1 by central IRF assessment or death from any cause, whichever occurs first. The censoring rules are described in Table 2 and Appendix 2.

Table 2: Censoring Rules for the Primary Analysis of PFS

Censoring Categories	Date of Censoring
Patients who did not have baseline or postbaseline tumor assessments and did not die on or before the data cutoff date	Randomization date
Patients who did not have radiographic progression as determined by IRF and did not die on or before the data cutoff date	Date of the last adequate tumor assessment on or before the data cutoff date
Patients who did not have radiographic progression as determined by IRF on or before initiation of a new antineoplastic therapy and did not die on or before the data cutoff date	Date of the last adequate tumor assessment on or before initiation of a new antineoplastic therapy and on or before the data cutoff date
Patients who had 2 or more consecutive missed scheduled tumor assessments immediately prior to disease progression	Date of the last adequate tumor assessment without evidence of disease progression before the 2 missed tumor assessments and on or before the data cutoff date
Patients who had the first radiographic progression as determined by IRF after the date of study drug discontinuation + 30 days and did not die on or before the data cutoff date	Date of the last adequate tumor assessment on or before the date of study drug discontinuation + 30 days and on or before the data cutoff date

IRF, independent review facility; PFS, progression-free surivival.

If a patient meets the criteria for more than 1 censoring rule, PFS will be censored at the earliest censoring date.

The primary analysis of PFS will be based on a stratified 2-sided log-rank test at a 0.05 significance level. Median PFS will be estimated for each treatment group using the Kaplan-Meier method and the 95% CIs will be calculated using the Brookmeyer-Crowley method (Brookmeyer & Crowley, 1992). The HR and the 95% CI will be estimated using a stratified Cox regression model with treatment group as the only main effect and the same stratification factors as the stratified log-rank test. An unstratified log-rank test and the HR and 95% CI from an unstratified Cox regression model will be presented as sensitivity analyses.

If the p-value for the stratified 2-sided log-rank test is statistically significant (< 0.05) and the estimated HR ($\lambda_{talazoparib}/\lambda_{physician's\ choice}$) is < 1, the null hypothesis of no difference in PFS will be rejected and it will be inferred that PFS is statistically longer in the talazoparib group compared with the control (physician's choice) group.

To evaluate the follow-up time for PFS between the 2 treatment groups, the median follow-up time for PFS will be estimated according to the Kaplan-Meier estimate of potential follow-up, also known as "Reverse Kaplan-Meier" (Schemper & Smith, 1996).

9.8.2.2 Sensitivity Analyses

Sensitivity analyses of PFS based on different definitions of progression events and censoring rules are described in this section and Appendix 2. These analyses will be performed for the ITT population, using the same statistical methods as the primary analysis.

1. Impact of investigator radiographic assessment: To evaluate PFS by investigator assessment of radiographic progression, the PFS analysis includes progression events by investigator assessment of radiographic progression or deaths. Clinical deterioration as assessed by investigator or radiographic progression determined by the IRF will not be considered progression events.
2. Impact of investigator radiographic and clinical deterioration assessments: To evaluate PFS by investigator assessments, the PFS analysis includes progression events of radiographic progression or clinical deterioration as assessed by investigator or death. Clinical deterioration will be determined by clinical review of treatment discontinuation reason recorded on the End of Treatment eCRF.
3. Impact of clinical deterioration by investigator: To evaluate clinical deterioration by investigator assessment, the PFS analysis includes radiographic progression as determined by IRF, clinical deterioration as assessed by investigator, or death. Clinical deterioration will be determined by clinical review of treatment discontinuation reason recorded on the End of Treatment eCRF.
4. Impact of radiographic progression after study drug discontinuation + 30 days: Patients who had radiographic progression as determined by IRF after 30 days following treatment discontinuation will also be considered to have a PFS event. For this analysis, PFS events include radiographic progression as determined by IRF that occurs anytime (on, before, or after 30 days following treatment discontinuation) or death due to any cause.
5. Impact of treatment discontinuation for any reason: Patients who discontinued study treatment before radiographic progression as determined by IRF or death will be considered to have a PFS event at the time of the study treatment discontinuation. For this analysis, PFS is defined as the time from randomization until the date of radiographic progression as determined by IRF, study treatment discontinuation for any reason, or death due to any cause, whichever occurs first.
6. Impact of postbaseline antineoplastic therapies: Patients who received any postbaseline antineoplastic therapy will be considered to have a PFS event. For this analysis PFS is defined as the time from randomization until the date of radiographic progression as determined by IRF, initiation of a new antineoplastic therapy, or death due to any cause, whichever occurs first.
7. Impact of on-study radiotherapy: For patients who received any on-study radiotherapy before radiographic progression as determined by IRF, PFS will be censored on the date of the last adequate tumor assessment on or before the radiotherapy. Date of on-study radiotherapy will be derived from the Prior and Concomitant Radiation Cancer Treatment eCRF.
8. Impact of deaths after end of treatment + 126 days (2 scheduled scans, every 9 weeks after week 30): For patients who did not have radiographic progression and died more

than 126 days following treatment discontinuation, PFS will be censored on the date of the last adequate tumor assessment on or before 126 days following treatment discontinuation.

9. Impact of capsule strength: Patients treated with a starting dose of 4 × 0.25 mg capsules will be excluded from this analysis. The treatment effect will be assessed in patients treated with a starting dose of 1 × 1 mg capsules.
10. Impact of central genetic testing: This PFS by IRF analysis will include only the subgroup of patients with a deleterious or suspected deleterious germline BRCA mutation based on the FDA-approved MYRIAD BRACAnalysis® assay (QSR assay) or CLIA assay and will exclude patients with only a local result available..
11. Impact of assessing eligibility with QSR assay: This PFS by IRF analysis will include only the subgroup of patients with a deleterious or suspected deleterious germline BRCA mutation based on the MYRIAD BRACAnalysis® assay (QSR assay) result and will exclude patients enrolled based on a local test result or a CLIA result. Approximately 70% of the patients randomized in the study are expected to be included in this sensitivity analysis.

Additional Analyses:

As another analysis for PFS, the HR will be estimated using a stratified Cox regression model with treatment group and selected baseline prognostic factors as the main effects, and using the same stratification factors as the primary analysis. The prognostic factors include ECOG score (0 vs > 0), BRCA status (BRCA1 vs BRCA2), prior platinum treatment (yes vs no), and time from initial diagnosis of breast cancer to initial diagnosis of advanced breast cancer (< 12 months vs ≥ 12 months).

Evaluation of the Discordance Rate Between Investigator and IRF on Assessing PFS Data

Potential evaluation bias between the investigator and IRF assessments will be assessed with respect to either disease progression status or the timing at which progression occurs using 2 measures, the early discrepancy rate and late discrepancy rate (Amit et al, 2011). The agreement between the investigator and IRF within a treatment arm is described as follows:

Investigator	Independent Radiology Facility	
	PD	No PD
PD	a=a1+a2+a3	b
No PD	c	d

Note: In practice, an investigator PD occurring later than an IRF assessed PD (a2) would rarely be observed.

a1 = number of agreements on timing and occurrence of PD.
a2 = number of times investigator declares PD later than IRF.
a3 = number of times investigator declares PD earlier than IRF.
b = number of subjects whose investigator declared PD but IRF did not.
c = number of subjects whose IRF declared PD but investigator assessment did not.
d = number of subjects neither investigator nor IRF assessments declared PD.

The early discrepancy rate (EDR) is defined as:

$$EDR = (b + a3) / (a + b)$$

The EDR represents the positive predictive value of investigator assessment and quantifies the frequency with which the investigator declares progression early relative to IRF within each arm as a proportion of the total number of investigator assessed PD's.

The late discrepancy rate (LDR) is defined as:

$$LDR = (c + a2) / (b + c + a2 + a3)$$

The LDR quantifies the frequency that investigator declares progression later than IRF as a proportion of the total number of discrepancies within the arm. If the distribution of discrepancies is similar between the arms, then this suggests the absence of evaluation bias favoring a particular arm.

The EDR and LDR can be calculated for each treatment arm and the differential discordance around each measure can be defined as the rate on the experimental arm minus the rate on the control arm. A negative differential discordance for the EDR and/or positive differential discordance for the LDR are suggestive of a bias in the investigator favoring the experimental arm.

In addition, the time to first, second, third, fourth, etc., tumor assessment visits will be summarized by treatment group using the median and the 95% CI. The number of missing tumor assessments will be summarized based on investigator and IRF assessment.

9.8.3 Secondary Efficacy Endpoints

The key secondary efficacy endpoint is OS. If the primary PFS test meets statistical significance at a level of 0.05, then a descriptive interim analysis of OS will be performed at

the time of the PFS analysis. The final OS analysis will be performed after approximately 321 deaths occur.

9.8.3.1 Objective Response Rate

The ORR is defined as the proportion of patients with a partial response (PR) or complete response (CR) as defined by RECIST v1.1 in the ITT with measurable disease population. Patients who do not have any postbaseline tumor assessments will not be considered responders. Confirmation of response by subsequent tumor assessment (at least 4 weeks) is not required.

The primary analysis of ORR will be performed using investigator assessment. Sensitivity analyses using IRF assessments will also be performed. These analyses will be conducted using the ITT with measurable disease population as follows:

1. Objective response by investigator: Patients with a best overall response (BOR) of PR or CR by investigator assessment at the data cutoff date will be considered responders.
2. Confirmed objective response by investigator: Patients with a BOR of PR or CR, confirmed by a subsequent tumor assessment (at least 4 weeks later) by investigator assessment at the data cutoff date will be considered responders.
3. Objective response based on best BOR of the 2 IRF readers: Patients with a BOR of PR or CR by 1 of the 2 IRF readers at the data cutoff date will be considered responders (details in Appendix 3).
4. Objective response based on worst BOR of the 2 IRF readers: Patients with a BOR of PR or CR by both IRF readers at the data cutoff date will be considered responders (details in Appendix 3).

As an additional sensitivity analysis, the ORR analysis will also be conducted using the ITT population.

Per the Independent Efficacy Review charter v3.0 dated 19 August 2016, an adjudicated BOR was not collected. Therefore, a single objective response by IRF is not available, and sensitivity analyses 3 and 4 presented above are proposed.

The stratified Cochran-Mantel-Haenszel method at a 0.05 significance level will be used for hypothesis testing of ORR by investigator between the 2 treatment groups. An unstratified p-value will also be provided as a sensitivity analysis.

Point estimates of ORR, the difference in response rates between the 2 treatment groups, and the 95% CIs for the point estimates and the difference will be provided. Confidence intervals will be calculated using exact methods. Odds ratios for ORR under treatment with physician's choice versus ORR under treatment with talazoparib, as well as 95% CIs will be provided.

For patients with lesions observed on the baseline brain scan, an intracranial ORR will be assessed. The following lesions will be considered intracranial:

- The anatomical location includes "brain" or "CNS"
- The lesion location = OTHER and the anatomical location includes "occipital" or "frontal" or "parietal" or "temporal"

Tumor response will be separately assessed by RECIST 1.1 following only intracranial target and non-target lesions.

BOR rates will be summarized by the number and percentage of patients within each response category (CR, PR, stable disease, progressive disease [PD], or not evaluable) for the ITT population, for the ITT with measurable disease population, and for patients in the ITT population who have non-measurable disease at baseline. Stable disease must be documented by at least 1 tumor assessment that occurred ≥ 6 weeks after randomization.

Clinical benefit rate at 24 weeks (CBR24) by investigator assessment will be compared between the 2 treatment groups for all patients in the ITT population. CBR24 is defined as the proportion of patients with a BOR of CR, PR, or stable disease lasting ≥ 24 weeks from randomization per RECIST v1.1 as determined by investigator. Patients who do not have any postbaseline tumor assessments will not be considered responders. A point estimate of CBR24 weeks and the exact 95% CI will be provided.

9.8.3.2 Overall Survival

Overall survival (OS) is defined as the time from randomization to death due to any cause. For patients without a death date at the time of data cutoff or permanently lost to follow-up, OS will be censored at the date the patient was last known to be alive on or before the data cutoff date. The date a patient was last known to be alive before the data cutoff date is described in Appendix 4.

OS (months) = (earliest date of death or censoring – date of randomization + 1)/30.4375

An interim analysis of OS will be conducted at a 0.0001 significance level on the ITT population at the time of the primary analysis of PFS. The median OS will be estimated for each treatment group using the Kaplan-Meier method and the 95% CIs will be calculated using the Brookmeyer-Crowley method. The HR and the 95% CI will be estimated using a stratified Cox regression model. No formal hypothesis testing will be performed for OS.

The final analysis of OS will be conducted when approximately 321 deaths occur. This analysis of OS will be conducted using the stratified 2-sided log-rank test using the ITT population. Median OS will be estimated for each treatment group using the Kaplan-Meier method and the 95% CIs will be calculated. The HR will be estimated using a stratified Cox regression model with treatment group as the only main effect. An un-stratified log-rank test, a stratified Wilcoxon's rank sum test, and the HR and 95% CI from an un-stratified Cox regression model will be presented as sensitivity analyses.

At the final analysis of OS, if the p-value for the stratified 2-sided log-rank test is significant at the level pre-specified in Section 9.8.1 and the estimated HR ($\lambda_{talazoparib}/\ \lambda_{physician's\ choice}$) is < 1, it will be inferred that OS is prolonged in the talazoparib group compared with the physician's choice group.

To assess the impact of postbaseline treatment with platinum or PARP inhibitor on OS, the following sensitivity analyses will be performed:

- Censor OS at the date of initiation of postbaseline platinum and/or PARP inhibitor treatment
- Use inverse probability of censoring weighting approach (Robins & Finkelstein, 2000) to correct for bias from switching treatment to platinum or PARP inhibitor. Key baseline characteristics and time-dependent variables predicting postbaseline treatment with platinum or PARP inhibitor will be considered in this approach.

As another analysis for OS, the HR will be estimated using a stratified Cox regression model with treatment group and selected baseline prognostic factors as the main effects. The prognostic factors include ECOG score (0 vs > 0), BRCA status (BRCA1 vs BRCA2), prior platinum treatment (yes vs no), and time from initial diagnosis of breast cancer to initial diagnosis of advanced breast cancer (< 12 months vs ≥ 12 months). This analysis will be performed using the ITT population.

9.8.4 Subgroup Analyses

To assess the robustness of treatment effects across subgroups, subgroup analyses will be conducted as appropriate for PFS and ORR at the analysis of PFS (when approximately 288 PFS events occur) and for OS at the final analysis of OS (when approximately 321 deaths occur). The following variables will be used to define subgroups:

- Age (< 50 years vs ≥ 50 years)
- Race (white vs other)
- Geographic region (North America [United States and Canada], Europe [Belgium, France, Germany, Ireland, Italy, Poland, Spain, United Kingdom, Russia, Ukraine, Israel], or rest of the world
- ECOG Score (0 vs > 0)
- BRCA status (BRCA1 vs BRCA2) by central laboratory analysis*
- Triple-negative status (yes vs no) derived from eCRF
- History of CNS metastasis (yes vs no) derived from eCRF
- Measurable disease by investigator (yes vs no)
- Visceral disease by investigator (yes vs no)
- Number of prior cytotoxic chemotherapy regimens for metastatic disease (0, 1, or > 1) derived from eCRF
- Prior neoadjuvant/adjuvant therapy (yes vs no)
- Prior capecitabine treatment (yes vs no)
- Prior platinum treatment (yes vs no)

- Prior hormonal/aromatase inhibitor treatment (yes vs no)
- Prior CDK4/6 inhibitors
- Time from initial diagnosis of breast cancer to initial diagnosis of advanced breast cancer (< 12 months vs ≥ 12 months)
- Prior regimens of cytotoxic chemotherapy for advanced breast cancer (0, 1 or 2+)
- Patients randomized under the original protocol versus patients randomized under protocol amendment 1. This analysis will address the impact of Protocol Amendment 1. The 14Dec2015 protocol amendment expanded the eligible patient population to allow stable disease for ≥6 months (previously was ≥12 months) after last dose of platinum in the adjuvant setting, 3 prior cytotoxic regimens, prior platinum-based therapy for advanced breast cancer (without documented disease progression), de novo Stage IV disease, and an ECOG performance status of 2.
- Patients with central genetic testing available (deleterious or suspected deleterious germline BRCA mutation by MYRIAD*) vs patients with local genetic testing available (deleterious or suspected deleterious germline BRCA mutation by a local genetic test approved by the sponsor). This analysis will address the impact of central versus local genetic testing.
  - *BRCA mutation status as per central laboratory confirmation using the FDA-approved Myriad BRACAnalysis® assay is reported as CDx results in the summary tables. This test is being filed contemporaneously as the CDx for this therapeutic agent.
- Patients treated with a starting dose of 1 × 1 mg capsules versus patients treated with a starting dose of 4 × 0.25 mg capsules. This analysis will address the impact of the capsule strength.

The subgroup analyses will use unstratified log-rank tests of PFS, and OS, For PFS and OS, median time will be estimated for each subgroup by treatment using the Kaplan-Meier method and the 95% CI will be calculated. In addition, the HR and the 95% CI will be estimated using an un-stratified Cox regression model and displayed in a forest plot.
The subgroup analyses will use a chi-square test for ORR. The ORR estimate and 95% CI will be displayed by treatment group. The odds ratio and 95% CI will be displayed within the subgroup.

9.8.5 Exploratory Efficacy Endpoints

9.8.5.1 Duration of Response

DOR is defined as the time from the first radiographic documentation of PR or CR to radiographic disease progression per RECIST v1.1 by investigator assessment or to death due to any cause, whichever occurs first. It will be summarized for patients with an objective response as determined by the investigator. Dates of progression and censoring will be determined as described for the sensitivity analysis of PFS by investigator radiographic assessment.

> DOR (months) = (earliest date of progression, death, or censoring – date of first documented objective response + 1)/30.4375

The median DOR will be estimated for each treatment group using the Kaplan-Meier method and the 95% CI will be calculated.

9.8.5.2 Time to End of First Post Study Therapy

Time to end of first post study therapy is defined as the time from randomization to the end date of the first post study antineoplastic therapy after the first documented disease progression by investigator assessment while on study treatment (talazoparib or PCT). The analysis of time to end of first post study antineoplastic therapy will be conducted using the ITT population.

Patients who died before initiating the first post study therapy will be considered to have an event on the date of death for the purpose of this endpoint. Patients for which only one post-study antineoplastic therapy was initiated after the first documented disease progression, and who died without an end date for the antineoplastic therapy, will be considered to have an event on the date of death for the purpose of this endpoint.

For patients who did not have a documented first disease progression on study 673-301, time to end of first post study antineoplastic therapy will be censored on the date of the permanent discontinuation of study drug or at the last tumor assessment with an overall assessment other than nonevaluable as determined by the investigator on or before the analysis data cutoff date, whichever comes later. For patients with a documented first disease progression on study drug who did not start any post study therapy, time to end of first post study therapy will be censored on the date of the permanent discontinuation of study drug or last tumor assessment available (with an overall assessment other than unevaluable), whichever comes last. For patients who started a post study antineoplastic therapy (after first disease progression), discontinued the study and did not have an end date for the first post study antineoplastic therapy before data cutoff date, time to end of first post study therapy will be censored on the date of the study discontinuation or on the date of the last available tumor assessment on or before the analysis data cutoff date, whichever comes later.

For patients who started a post study antineoplastic therapy (after first disease progression on study drug), did not discontinued the study and the first post study antineoplastic treatment is ongoing at the analysis data cutoff date, the time to end of first post study therapy will be censored on the analysis data cutoff date.

Kaplan-Meier methods will be used for calculating the median time to end of first subsequent therapy for both treatment arms. A 2-sided 95% CI will be provided for this estimate.
A Cox proportional hazards model will be used to calculate the hazard ratio and its 95% CI.

9.8.5.3 Quality of Life

All patients randomly assigned to study treatment will be asked to complete the EORTC QLQ-C30 and QLQ-BR23 at protocol-specified time points.

9.8.5.3.1 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 3. The full questionnaire is provided in protocol Section 24.4.

Table 3: 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 as shown in Table 4. The full QLQ-BR23 is provided in protocol Section 24.4.

Table 4: 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 nonmissing. If less than half of the items are nonmissing, 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.

9.8.5.3.2 EORTC QLQ –C30 and QLQ-BR23 Analysis

Analyses of the EORTC data will be conducted by treatment as randomized for all patients in the PRO-evaluable population with the exception of completion table which will be conducted on the ITT population.

The completion table will display the number and percentage of patients in each treatment group at each time point who completed these instruments. An instrument is considered completed if at least one item was answered by the patient.

Descriptive statistics (mean, standard deviation, 95% CI, median, range) of observed values and changes from baseline for each treatment group and differences between groups at each time point will be presented for each of the 15 scales of EORTC QLQ-30, as well as each of the 8 scales of the EORTC QLQ-23.

A detailed data listing supporting the descriptive statistics will also be provided.

For the Global Health Status/QOL scale of the EORTC QLQ-C30 and the breast symptoms scale of the EORTC QLQ-B23, the statistical comparison between the two treatment groups will be based on a longitudinal repeated measures analysis using a mixed effects model. The variables in the model will be treatment, time, treatment-by-time, with baseline used as a covariate. Parameter estimates will be based on a restricted maximum likelihood method. No adjustments for multiple comparisons will be made.
In addition, the Global Health Status/QOL from the EORTC QLQ-C30 and the breast symptoms scale from EORTC QLQ-BR23 will also be explored using survival analysis methods comparing the 2 treatment groups on time to deterioration:

- Time to deterioration in Global Health Status/QOL is defined as the time from randomization to the first observation with a ≥10 point decrease and no subsequent observations with a <10 point decrease from baseline.

- Time to deterioration in QLQ-BR23 breast symptoms scale is defined as the time from randomization to the first observation with a ≥10 point increase and no subsequent observations with a <10 point increase from baseline.

- The analysis of these 2 endpoints will be based on a stratified 2-sided log-rank test at a 0.05 significance level. Median time to deterioration will be estimated for each treatment group using the Kaplan-Meier method and the 95% CIs will be calculated using the Brookmeyer-Crowley method (Brookmeyer & Crowley, 1992). The HR and the 95% CI will be estimated using a stratified Cox regression model with treatment group as the only main effect and the same stratification factors as the stratified log-rank test. An unstratified log-rank test and the HR and 95% CI from an unstratified Cox regression model will also be presented. Kaplan-Meier plots will be provided.

9.9 Pharmacokinetic Analysis

Analyses of the PK data will be conducted using the PK population.

Summary statistics will be provided for plasma talazoparib concentrations at scheduled visits. Plasma concentration values below the limit of quantitation will be treated as zero in the descriptive statistics calculations. The summary table will include the number of patients, number of samples with values below the limit of quantitation, mean, standard deviation, percent coefficient of variation (%CV), 95% CI, median, minimum, maximum, geometric mean, and geometric %CV.

The PK data from this study will be combined with PK data from other studies to develop a population PK model and will be used to estimate PK parameters for each individual patient . These individual PK parameter estimates will then be used to estimate individual exposure parameters (eg, area under the concentration time curve over a dosing interval [AUC_{τ}], accumulative AUC, maximum concentration [C_{max}], and minimum concentration [C_{min}]). The association between talazoparib exposure parameters and efficacy and safety outcomes will be explored. These analyses will be specified in a separate population PK and exposure-response analysis plan.

9.10 Safety Analyses

All safety analyses will use the safety population, summarized by the actual treatment received.

9.10.1 Adverse Events

Adverse events will be coded using MedDRA, in accordance with the version(s) documented in the data management plan. Adverse events will be classified by severity using the CTCAE v 4.03.

Only treatment-emergent adverse events (TEAEs) with an onset date on or after the date of first dose of study drug and before the date of last dose + 30 days or before the date of initiation of a new antineoplastic therapy (whichever occurs first) will be included in the adverse event summaries. A TEAE is defined as any adverse event that newly appeared or worsened in severity following initiation of the study drug administration. Summaries of treatment-emergent period length will be provided.

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. If relationship to study drug is missing, the adverse event will be counted as related. Adverse event listings will show missing relationship as missing.

Adverse event time-adjusted rates will be calculated as the number of occurrences of an event divided by the number of patient-years of treatment-emergent surveillance for each treatment group. Patients can have more than 1 occurrence of each event. Adverse events that are continuous but change in severity, relationship, or seriousness will be counted as 1 event.

Tabular summaries with numbers and percentages of patients that have the following adverse events will be provided:

- Overview of TEAEs
- All TEAEs
  - By system organ class and preferred term
  - By decreasing frequency of preferred term
  - By system organ class, preferred term, and maximum severity
  - By decreasing frequency of preferred term per 100 patient-years
- 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
  - By decreasing frequency of preferred term per 100 patient-years
- TEAEs leading to study drug discontinuation
  - By system organ class and preferred term
  - By decreasing frequency of preferred term
- TEAEs other than progressive disease, leading to study drug discontinuation
  - By system organ class and preferred term
  - By decreasing frequency of preferred term
- TEAEs leading to dose reduction
  - By system organ class and preferred term
  - By decreasing frequency of preferred term

  - By system organ class, preferred term, and maximum severity
- TEAEs leading to dose interruption
  - By system organ class and preferred term
  - By decreasing frequency of preferred term
  - By system organ class, preferred term, and maximum severity
- 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
  - With action taken of permanent discontinuation of study drug by system organ class, preferred term, and maximum severity
  - Leading to study drug discontinuation by system organ class and preferred term

The time to first grade 3 or 4 TEAE and the time to first serious TEAE, by treatment group, will be displayed using Kaplan-Meier methods. Data from patients without a reported grade 3 or higher (or serious) TEAE by the data cutoff date will be censored at the end of the treatment-emergent period or data cutoff date (whichever occurs first).

Subgroup tabulations of TEAEs, grade 3 or 4 TEAEs, and serious TEAEs by treatment group (talazoparib vs. overall physician's choice), will be created as shown in Table 5.

Table 5: Subgroup Tabulations of Treatment-Emergent Adverse Events

Group Variable	Subgroups	Definitions
Study Day Cut Points	≤ 30 days after initiation of study treatment 31-180 days after initiation of study treatment 181 - 365 days after initiation of study treatment	Adverse events will be assigned to day categories based on the study day of the adverse event start date (or worsening date). The study day will be calculated as shown in Section 7.3.
Age (years)	< 50 vs ≥ 50 < 65 vs ≥ 65	
Baseline body mass index	BMI≤ 18 18<BMI≤30 BMI> 30	
Geographic region	North America Europe Rest of the world	

9.10.1.1 Identified Risks and General Safety Topics

The following identified risks and general adverse events will be summarized for the overall safety population and by decreasing frequency of preferred term for each treatment group:

Identified Risks

- Myelosuppression, as defined by the Standardized MedDRA Query (SMQ) of 'cytopenia'

General Safety – Adverse events of interest

- Myelodysplastic syndrome, as defined by the SMQ of 'myelodysplastic syndrome (MDS)'
- Acute myeloid leukemia as defined by the collection of preferred terms included in Appendix 6
- Hepatotoxicity, as defined by the narrow SMQ of 'drug related hepatic disorders comprehensive search'

Kaplan-Meier analyses may be performed to explore the time from the first dose of study drug to onset of the first adverse event of interest (AML/MDS, myelosuppression, hepatic impairment) if a sufficient number of events occur. Data from patients without adverse events of interest will be censored at the date of the last adequate safety assessment on or before the data cutoff date.

9.10.2 Deaths

The number of patients who died (within 30 days after the last dose and more than 30 days after the last dose) and causes of death will be summarized by treatment group for the safety population. Deaths will be summarized and listed based on the Death eCRF.

9.10.3 Clinical Laboratory Tests

Clinical laboratory data were collected for this study using local laboratory testing. More than 1 local laboratory could be used per study site, per patient, and/or per time point.

The following key laboratory parameters will be summarized: hemoglobin, leukocytes, lymphocytes, neutrophils, platelets, hematocrit, alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, bilirubin, blood urea nitrogen, creatinine.

For each key clinical laboratory measurement, descriptive statistics will be provided for the baseline value and all subsequent postbaseline scheduled time points. Changes from baseline to postbaseline values will also be provided.

For each key laboratory parameter that is gradable by the CTCAE, a shift table will be provided to summarize baseline versus worst postbaseline toxicity grade during the treatment-emergent period. The number and percentage of patients with grade 3 or 4 laboratory values in the treatment-emergent period will be summarized. The number and percentages of patients with a toxicity grade increase of 2 or more above baseline will also be summarized.

The number and proportion of patients with liver test elevations will be presented by treatment group. Liver function test elevations will be assessed using postbaseline results for alanine aminotransferase, aspartate aminotransferase, total bilirubin, and alkaline phosphatase from the treatment-emergent period per Table 6.

Table 6: Categories of Liver Test Elevations

Laboratory Test Category	Category
ALT, AST, TBL, or ALP	Postbaseline ALT or AST ≥ 3 × ULN Postbaseline ALT or AST >5 × ULN Postbaseline AST or ALT >10 × ULN Postbaseline AST or ALT >20 × ULN
	TBL > 2 × ULN
	Postbaseline ALT or AST ≥ 3 × ULN and TBL > 2 × ULN (at any visit)
	Postbaseline ALT or AST ≥ 3 × ULN and TBL > 2 × ULN and ALP < 2 × ULN (at any visit)
	Postbaseline ALT or AST ≥ 3 × ULN and TBL > 2 × ULN (concurrent or within 14 days)
	Postbaseline ALT or AST ≥ 3 × ULN and TBL > 2 × ULN and ALP < 2 × ULN (concurrent or within 14 days)

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBL, total bilirubin; ULN, upper limit of normal.

9.10.4 Vital Signs and Weight

Systolic and diastolic blood pressure, heart rate, weight, and temperature will be summarized at baseline and at all subsequent scheduled time points. Changes from baseline value will be presented for all scheduled time points. All recorded vital sign data will be listed.

The number and percentage of patients with the following vital sign changes based on observed data will be presented by treatment group:

- Systolic blood pressure:
  - Absolute results >180 mmHg and increase from baseline ≥ 40 mmHg
  - Absolute results <90 mmHg and decrease from baseline >30 mmHg
- Diastolic blood pressure:
  - Absolute results >110 mmHg and ≥ 30 mmHg increase from baseline
  - Absolute results <50 mmHg and >20 mmHg decrease from baseline
  - ≥ 20 mmHg increase from baseline
- Heart rate > 120 beats per minute (bpm) and > 30 bpm increase from baseline
- Heart rate < 50 bpm and > 20 bpm decrease from baseline
- Weight >10% decrease from baseline

9.10.5 Electrocardiograms

ECG findings will be listed.

9.10.6 ECOG Performance Status

A shift table will be provided to summarize baseline versus worst postbaseline ECOG performance status score. The ECOG performance status scores will also be listed.

9.10.7 Physical Examination

Physical examination findings will be listed.

9.10.8 Serum Pregnancy Testing

Female patients of childbearing potential will have serum pregnancy tests as specified in the protocol. Serum pregnancy testing results will be listed.

10 CHANGES FROM PROTOCOL IN STUDY CONDUCT OR STATISTICAL ANALYSIS PLAN (V3.0)

- The definition of duration of exposure for talazoparib and each of 4 physician's choice therapies was clarified (Section 9.7)
- The multiplicity adjustment for efficacy analyses was modified to include PFS by IRF and OS in order to allow statistical testing of OS at final analysis at 0.0499 level (Section 9.8.1)
- The sensitivity analysis assessing the impact of central genetic testing was clarified to include all patients for which there is a central genetic testing result available (using the QSR assay or the CLIA assay). In addition, the following pre-planned sensitivity analysis for the primary endpoint (rPFS) was added (Section 9.8.2.2):
  - Impact of assessing eligibility with QSR assay: This PFS by IRF analysis will include only the subgroup of patients with a deleterious or suspected deleterious germline BRCA mutation based on the MYRIAD BRACAnalysis® assay (QSR assay) result and will exclude patients enrolled based on local test result or CLIA result. It is expected that ~70% of the patients randomized in the study will be included in this sensitivity analysis.
- Clarification was added regarding rationale for 2 sensitivity analyses for ORR by IRF. As per imaging charter v3.0 dated 19 August 19, 2016, an adjudicated BOR and therefore a single ORR by IRF are not available (Section 9.8.3.1).
- The following pre-planned analyses were added for the breast symptoms scale of the EORTC QLQ-BR23 (Section 9.8.5.3.2):
  - longitudinal repeated measures analysis using a mixed effects model;
  - time to deterioration for breast symptom scale, defined as the time between baseline and the first observation with an increase meeting the threshold of 10 or more points and no subsequent observation not meeting this threshold increase.
- Summaries for TEAEs leading to dose modifications (including dose reductions and dose interruptions) were added (Section 9.10.1)
- Laboratory parameters that will be summarized were clarified (Section 9.10.3)

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Appendix 1: Imputation of Missing/Partially Missing Dates

Missing data will not be imputed unless otherwise specified.

For safety analyses, incomplete date of last dose of study drug and incomplete start date of a new antitumor treatment for breast cancer that are missing the day of the month, the 15th of the month will be used to impute the missing data. When imputing partial last dose dates, the last assessment date and death date will be taken into consideration. This imputation rule will be used to determine the treatment-emergent period.

Adverse Events and Concomitant Medications

The imputation rule for the safety analyses will be used to address the issues with partial dates. The imputed dates will be used to determine the treatment-emergent period. For adverse events with a partial date, available date parts (year, month, and day) of the partial date will be compared with the corresponding date components of the start date and end date of the treatment-emergent period to determine if the event is treatment emergent. When in doubt, the adverse event will be considered treatment emergent by default. The following rules will be applied to impute partial dates for adverse events:

If start date of an adverse event is partially missing, impute as follows:

- If both month and day are missing and year = year of treatment start date, then set to treatment start date
- If both month and day are missing and year ≠ year of treatment start date, then set to January 01
- If day is missing and month and year = month and year of treatment start date, then set to treatment start date
- If day is missing and month and year ≠ month and year of treatment start date, then set to first of the month
- If start date is completely missing, set to treatment start date as long as adverse event end date is not before treatment start date

If end date of an adverse event is partially missing, impute as follows:

- If both month and day are missing, then set to December 31
- If only day is missing, then set to last day of the month
- If end date is completely missing, do not impute

When the start date or end date of a medication is partially missing, the date will be imputed to determine whether the medication is prior or concomitant (or both). The following rules will be applied to impute partial dates for medications:

If start date of a medication is partially missing, impute as follows:

- If both month and day are missing, then set to January 01
- If only day is missing, then set to the first of the month

If end date of a medication is partially missing, impute as follows:

- If both month and day are missing, then set to December 31
- If only day is missing, then set to last day of the month

If start date or end date of a medication is completely missing, do not impute.

Diagnosis of Breast Cancer

If the diagnosis date of breast cancer is partially missing, the following rules will be applied to impute partial dates:

- If both month and day are missing and year = year of treatment start date, then set to treatment start date.
- If both month and day are missing and year ≠ year of treatment start date, then set to December 31.
- If day is missing and month and year = month and year of treatment start date, then set to treatment start date.
- If day is missing and month and year ≠ month and year of treatment start date, then set to the last day of the month.

Appendix 2: Definition of Progression-Free Survival

Progression-free survival (PFS) is defined as time from randomization until the date of radiologic progressive disease per the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) by central independent radiology facility (IRF) assessment or death from any cause, whichever occurs first. Patients who die after receiving the first dose of study drug on or before the data cutoff date without postbaseline tumor assessments or without radiographic progression as determined by the IRF will be considered to have a PFS event on the date of death.

The censoring rules for the primary and sensitivity analyses of PFS are summarized in the following table; the earliest applicable censoring time will be used:

Analysis	Censoring Rules	Date of Censoring
Primary analysis of PFS	Patients who did not have baseline or postbaseline tumor assessments and did not die on or before the data cutoff date	Randomization date
	Patients who did not have radiographic progression as determined by IRF and did not die on or before the data cutoff date	Date of the last adequate tumor assessment on or before the data cutoff date
	Patients who did not have radiographic progression as determined by IRF on or before initiation of a new antineoplastic therapy and did not die on or before the data cutoff date	Date of the last adequate tumor assessment on or before initiation of a new antineoplastic therapy and on or before the data cutoff date
	Patients who had 2 or more consecutive missed scheduled tumor assessments immediately prior to disease progression	Date of the last adequate tumor assessment without evidence of disease progression before the 2 missed assessments and on or before the data cutoff date
	Patients who had the first radiographic progression as determined by IRF after the date of study drug discontinuation + 30 days and did not die on or before the data cutoff date	Date of the last adequate tumor assessment on or before the date of study drug discontinuation + 30 days and on or before the data cutoff date

IRF, independent radiology facility; PFS, progression-free survival.

Sensitivity Analyses: Only specific censoring/ event rules that are different from the primary analysis are described here	
PFS based on investigator assessment	**Date of Censoring**
Censoring rules are the same as the primary analysis	
Impact of investigator radiographic and clinical deterioration assessments	**Date of Censoring**
Censoring rules are the same as the primary analysis	
Impact of clinical deterioration by investigator	**Date of Censoring**
Clinical deterioration is a PFS event. Censoring rules are the same as the primary analysis.	
Impact of radiographic progression after study drug discontinuation + 30 days	**Date of Progression**
Radiographic progression on, before, and after 30 days following study drug discontinuation and death will be considered PFS events.	
Impact of treatment discontinuation for any reason	**Date of Progression**
Patients who discontinued study treatment without evidence of disease progression as determined by IRF or death	Last dose date
Impact of postbaseline antineoplastic therapies	**Date of Progression**
Patients who received a new antineoplastic therapy without radiographic progression as determined by IRF or death	Date of initiation of new antineoplastic therapy
On-study radiotherapy	**Date of Censoring**
Radiographic disease progression as determined by IRF after on study radiotherapy	Date of last adequate tumor assessment without evidence of disease progression on or before the radiotherapy
Impact of deaths after end of treatment + 126 days (2 scheduled scans)	**Date of Censoring**
Patients who died more than 126 days following study treatment discontinuation and before radiographic progression	Date of last adequate tumor assessment on or before 126 days following study treatment discontinuation

IRF, independent review facility; PFS, progression-free surivival.

Appendix 3: Best or Worst of Best Overall Response per Central Independent Radiology Facility Assessment

Best or worst of best overall response (BOR) as determined by the 2 central independent radiology facility readers will be derived as follows:

IRF Reader 1	IRF Reader 2	Best BOR	Worst BOR
CR	Any	CR	Reader 2 response
PR	PR, SD, Non-CR/Non-PD, PD, NE	PR	Reader 2 response
SD or Non-CR/non-PD	SD, Non-CR/Non-PD, PD, NE	SD	Reader 2 response Both Non-CR/Non-PD and SD will be categorized as SD
PD	PD or NE	NE	PD
NE	NE	NE	NE

BOR, best overall response; CR, complete response; IRF, independent radiology facility; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

Appendix 4: Overall Survival

For the overall survival analysis, deaths that occur on or before the data cutoff date will be considered an event. Data from patients who do not die on or before the data cutoff date will be censored at the last contact date. The last contact date will be derived as follows:

Source Data	Conditions
Date of randomization	No condition
Last contact date/last date patient known to be alive from Long-Term Follow-Up eCRF	• Use if patient status is reported to be alive • Do not use if patient status is reported unknown
Start/end dates of postbaseline antineoplastic therapy	Nonmissing medication/procedure term
Start/end dates from drug administration record	Nonmissing dose. Doses of 0 are allowed.
End of treatment date from the End of Treatment eCRF	No condition
Tumor assessment (RECIST v1.1) date	Evaluation is marked as done.
Laboratory/PK collection dates	Sample collection marked as done.
Vital signs date	At least 1 nonmissing parameter value
ECOG performance status date	Nonmissing ECOG performance status
Start/end dates of adverse events	Nonmissing verbatim term
Physical examination	At least 1 nonmissing parameter value
ECG	At least 1 nonmissing parameter value

ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report form; PK, pharmacokinetics; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Appendix 5: Visit Windows

Visit windows will be used to associate assessments with a scheduled visit for summarizing data by visit. Visit windows for safety and laboratory assessments are defined in the following tables.

Baseline value for safety and laboratory assessments is defined as last value before the date/time of first dose of study drug. Baseline value for quality of life (QOL) is defined as last assessment on or before the date of randomization. If more than 1 assessment occurs within a given visit window, the assessment closest to the target date will be used in summaries for the given visit. If 2 assessments are equally close to the target day, the earlier assessment will be used.

Visit Windows for Safety and Laboratory Assessments

Analysis Visit Name (AVISIT)	Start Day	Target Day	End Day
Hematology			
Week 2	2	8	11
Week 3	12	15	18
Week 4	19	22	25
Week 5	26	29	32
Week 6	33	36	39
Week x (x = 7, 8, 9, etc [every week])	(x − 1) × 7 − 2	(x − 1) × 7 + 1	(x − 1) × 7 + 4 [1]
End of Treatment [2]	Study day of last dose of study drug	Study day of last dose of study drug + 30	Study day of last dose of study drug + 40
Chemistry			
Week 4	2	22	32
Week 7	33	43	53
Week x (x = 10, 13, 16, etc [every 3 weeks])	(x − 1) × 7 − 9	(x − 1) × 7 + 1	(x − 1) × 7 + 11
End of treatment [2]	Study day of last dose of study drug	Study day of last dose of study drug + 30	Study day of last dose of study drug + 40
Vital Signs (systolic and diastolic blood pressure, heart rate, respiration rate, and temperature)			
Week 2	2	8	11
Week 3	12	15	18
Week 4	19	22	25
Week 5	26	29	32
Week 6	33	36	39
Week 7	40	43	53
Week x (x = 10, 13, 16, etc [every 3 weeks])	(x − 1) × 7 − 9	(x − 1) × 7 + 1	(x − 1) × 7 + 11 [1]
End of treatment [2]	Study day of last dose of study drug	Study day of last dose of study drug + 30	Study day of last dose of study drug + 40
Vital Signs (weight)			
Week 4	2	22	32
Week x (x = 7, 10, 13, etc [every 3 weeks])	(x − 1) × 7 − 9	(x − 1) × 7 + 1	(x − 1) × 7 + 11 [1]
End of treatment [2]	Study day of last dose of study drug	Study day of last dose of study drug + 30	Study day of last dose of study drug + 40

[1] Minimum of end day of week x and (study day of last dose of study drug - 1).

[2] Only includes data collected before any new antineoplastic therapy start date.

Visit Windows for QOL

Analysis Visit Name (AVISIT)	Start Day	Target Day	End Day
Week 4	2	22	32
Week x (x = 7, 10, 13, etc [every 3 weeks])	(x − 1) × 7 − 9	(x − 1) × 7 + 1	(x − 1) × 7 + 11 [1]
End of treatment [2]	Study day of last dose of study drug	Study day of last dose of study drug + 30	Study day of last dose of study drug + 40

[1] Minimum of end day of week x and (study day of last dose of study drug - 1).

[2] Only includes data collected before any new antineoplastic therapy start date.

Appendix 6: MedDRA v 18.0 Preferred Terms Included in Summaries for *Acute Myeloid Leukemia* as an Adverse Event of Interest

Acute leukaemia	Leukaemia cutis
Acute leukaemia in remission	Leukaemia granulocytic
Acute megakaryocytic leukaemia	Leukaemia in remission
Acute megakaryocytic leukaemia (in remission)	Leukaemia monocytic
Acute monocytic leukaemia	Leukaemia recurrent
Acute monocytic leukaemia (in remission)	Leukaemic cardiac infiltration
Acute myeloid leukaemia	Leukaemic infiltration
Acute myeloid leukaemia (in remission)	Leukaemic infiltration extramedullary
Acute myeloid leukaemia recurrent	Leukaemic infiltration gingiva
Acute myelomonocytic leukaemia	Leukaemic infiltration hepatic
Acute promyelocytic leukaemia	Leukaemic infiltration ovary
Acute undifferentiated leukaemia	Leukaemic infiltration pulmonary
Blast crisis in myelogenous leukaemia	Leukaemic infiltration renal
Bone marrow leukaemic cell infiltration	Leukaemic lymphoma
Erythroleukaemia	Monocytic leukaemia in remission
Leukaemia	Myeloid leukaemia
Leukaemia basophilic	Myeloid leukaemia in remission