Statistical Analysis Plan

Study ID: 213551

Official Title of Study: A phase III, randomized, open label, multicenter, controlled trial of niraparib versus physician's choice in previously-treated, HER2 negative, germline BRCA mutation-positive breast cancer patients.

Date of Document: 11 Aug 2020

Table 1: List of SAPs

SAP Version Number	SAP Title	Sponsor	Protocol Version	Date of Approval
1.0	Statistical Analysis Plan	TESARO[a]	6.0	11 August 2020
1.0	Statistical Analysis Plan	EORTC	6.0	24 January 2017

Abbreviations: EORTC= European Organisation for Research and Treatment of Cancer
[a] TESARO is a wholly owned subsidiary of GlaxoSmithKline Company

STATISTICAL ANALYSIS PLAN

A phase III, randomized, open label, multicenter, controlled trial of niraparib versus physician's choice in previously-treated, HER2 negative, germline BRCA mutation-positive breast cancer patients

Protocol Number:	PR-30-5010-C
Protocol Version and Date:	v6.0 January 13, 2017 v5.0 November 04, 2015 v4.0 May 04, 2015 v3.0 April 24, 2014 v2.0 August 28, 2013 v1.0 July 22, 2013 Outline January 28, 2013
Study Drug Name:	Niraparib and Physician's Choice (Eribulin, Vinorelbine, Gemcitabine and Capecitabine)
Phase:	Phase III
Sponsor:	TESARO, Inc. (a Glaxo Smith Kline Company)
Analysis Plan Date:	August 11, 2020
Analysis Plan Version:	Version 1.0

SPONSOR SIGNATURE PAGE

Protocol Title:	A phase III, randomized, open label, multicenter, controlled trial of niraparib versus physician's choice in previously-treated, HER2 negative, germline BRCA mutation-positive breast cancer patients
Protocol Number:	PR-30-5010-C
Sponsor:	TESARO, Inc., a Glaxo Smith Kline Company 1000 Winter Street Waltham MA 02451

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidance and guidelines.

PPD

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ABBREVIATIONS

Abbreviation	Explanation
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Plasma or Serum Concentration
AUC_{ss}	Area Under the Plasma or Serum Concentration at Steady State
BMI	Body Mass Index
CI	Confidence Interval
CL/F	Clearance After Oral Administration
C_{max}	Maximum Observed Plasma or Serum Concentration
$C_{max, ss}$	Maximum Observed Plasma or Serum Concentration at Steady State
C_{min}	Minimum Observed Plasma or Serum Concentration
$C_{min, ss}$	Minimum Observed Plasma or Serum Concentration at Steady State
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DOR	Duration of Response
ECG	Electrocardiography
ECOG	Eastern Cooperative Oncology Group
EQ-5D-5L	Euroqol 5 Dimension 5 Level
ER	Estrogen Receptor
GSK	Glaxo Smith Kline
HER-2	Human Epidermal Growth Factor Receptor 2
HRQoL	Health-Related Quality of Life
ID	Identifier
ITF	Time to Treatment Failure
ITT	Intent-To-Treat
IV	Intravenous(ly)
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NCCN	National Comprehensive Cancer Network
ORR	Overall Response Rate
OS	Overall Survival

PD	Progressive Disease
PDV	Important or Significant Protocol Deviation
PFS	Progression Free Survival
PRO	Patient Reported Outcomes
PT	Preferred Term
QD	Quaque Die (Once Daily)
QLQ-C30	Quality of Life Questionnaire C30
QoL	Quality of Life
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SOC	System Organ Class
STD	Standard Deviation
TEAE	Treatment Emergency Adverse Event
V_z/F	Volume of Distribution After Oral Administration
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) is designed to outline the statistical methods for evaluating the safety and efficacy of investigational drug niraparib for TESARO study protocol PR-30-5010-C: A phase III, randomized, open label, multicenter, controlled trial of niraparib versus physician's choice in previously-treated, HER2 negative, germline BRCA mutation-positive breast cancer patients.

This document has been prepared based on study protocol version 6.0 dated January 13, 2017. This SAP is intended to supplement but not supersede the core SAP issued by the European Organization for the Research and Treatment of Cancer (EORTC), approved on January 24, 2017 (Appendix 1).

2. STUDY DESIGN OVERVIEW

2.1. Overall Study Design

This study is a randomized, open-label, multicenter, controlled trial to compare niraparib versus physician's choice, amongst one of the following 4 single agents: eribulin, vinorelbine, gemcitabine or capecitabine, in patients with HER2-negative *gBRCA*mut breast cancer. Patients will be centrally registered at the EORTC Headquarters prior to the start of treatment, and after verification of the eligibility criteria, eligible patients will be randomized 2:1 to receive niraparib orally at a dose of 300 mg QD on a continuous dosing regimen or physician's choice amongst one of the following four single agents (eribulin, vinorelbine, gemcitabine, or capecitabine) according to the national available and approved treatment (gemcitabine will be administered as single agent as per NCCN guidelines. In France, gemcitabine is not allowed to be chosen as a treatment in the physician's choice arm).

The study schema is presented Figure 1.

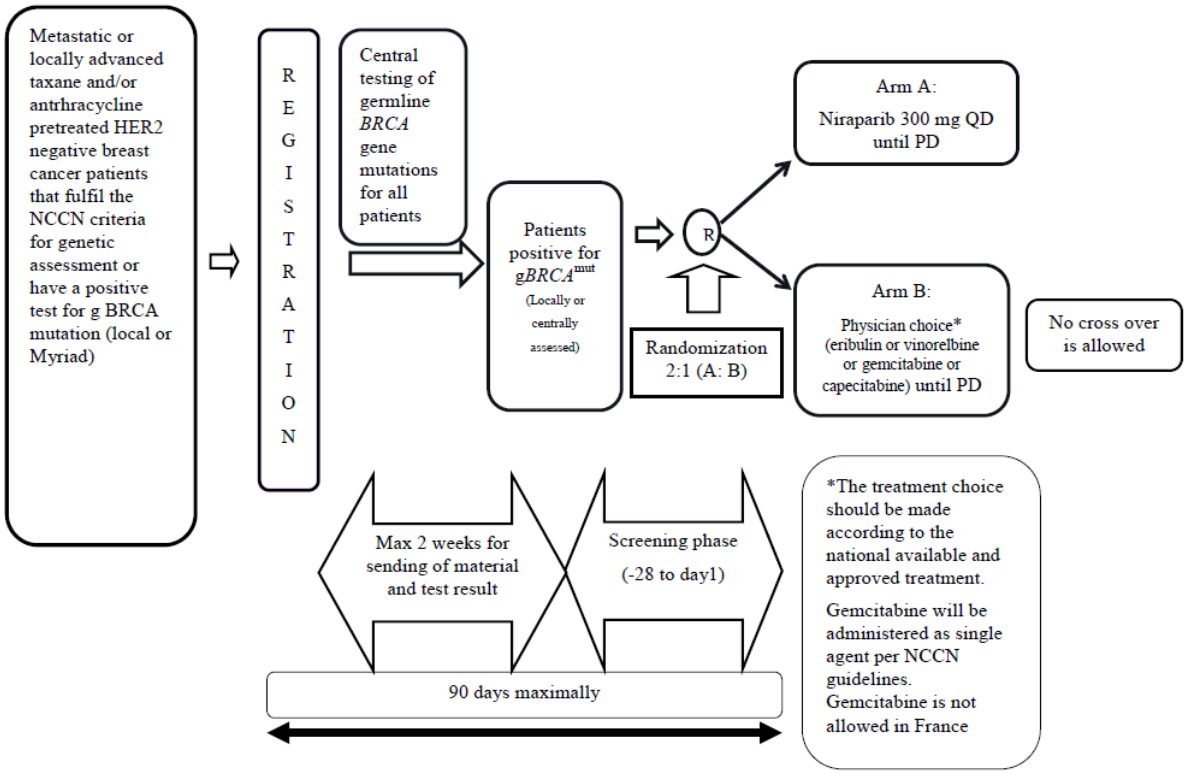
Screening assessments to determine patient eligibility for the study and to assess baseline disease status will be conducted within 28 days prior to the first dose (cycle 1/day 1). Clinic visits will be conducted at the beginning of every cycle (i.e., every 3 weeks ± 3 days). Contrast enhanced computed tomography (CT) or magnetic resonance imaging (MRI) if CT is not feasible will be required at screening and every 2 cycles (6 weeks ± 7 days) for the first 12 months, then every 3 cycles (9 weeks ± 7 days) until disease progression. Patients will continue their assigned treatment until disease progression (determined by Response Evaluation Criteria in Solid Tumors [RECIST] v.1.1), unacceptable toxicity, death, withdrawal of consent, or they are lost to follow-up.

Evaluation of CT scans and MRI, including determination of response to treatment and date of progression based on RECIST v.1.1, will be conducted by a central blinded review committee comprised of 2 radiologists, with an arbiter as necessary. Results of the central blinded assessment will be used to determine the primary efficacy endpoint of PFS and will be conducted retrospectively. The study investigators also will assess response to treatment and date of progression based on RECIST v.1.1 during the conduct of the study.

Patient reported outcomes (PROs) will be evaluated at screening, during the treatment period and after treatment discontinuation for a maximum period of up to 12 months after randomization. All patients randomized to niraparib will also undergo sparse blood sampling (predose and 2 hours postdose except for cycle 4, day 1 that will be done only predose) at specified study visits for measurement of plasma levels of niraparib and translational protocol specified analyses.

Safety will be evaluated throughout the study by adverse event (AE) monitoring and clinical laboratory assessments (hematology, chemistry), vital signs, electrocardiograms (ECGs), physical examinations, and use of concomitant medications.

Figure 1: Study Schema



After treatment discontinuation, information on subsequent anticancer therapy and survival (including new malignancy information) will be collected. If the patient discontinues prior to disease progression, tumor imaging, and assessment of PROs, will continue during the post-treatment phase at specified time intervals until disease progression or until the patient starts his/her subsequent anticancer therapy. No crossover to niraparib is permitted following discontinuation from physician's choice treatment.

The study schedule is summarized in Table 1.

Table 1: Summary Table

Cycle[1]	Registration	Screen	C1			C2		Subsequent cycles[2]	Study Medication Termination (to occur within 28 days of start of Last cycle)	Post- treatment follow-up		
										30-Day Follow- up	Every 6 weeks ± 7 days for the first 12 months and then every 9 weeks ± 7 days until PD or subsequent treatment	Follow-up every 3 months
Day	At any time prior to screening	-28 to day 1	D1	D8	D15	D1	D8	Cycle n, Day 1				
Informed Consents	X	X										
Demographics		X										
Medical, surgical, cancer, medication history		X										
Blood sample for g*BRCA* mutation analysis[3]	X											
Blood sample for companion diagnostic test[4]	X											
Archival tumor samples[5]		X	X									
Optional tumor biopsy[6]		X							X[6]		X[6]	
Pregnancy test[7]		X[7]										
Randomization		X[8]										
Physical examination		X	X			X		X	X			
Vital signs, height[9], weight		X	X			X		X	X			
ECOG performance status		X	X			X		X	X			
Adverse event monitoring	X[23]	X	X			X		X	X	X		
Collection of prior history of myelosuppression (i.e. anemia, neutropenia, leukopenia and thrombocytopenia)		X										
Serious adverse event monitoring	X[23]	X	X			X		X	X	X		
Concomitant medications		X	X			X		X	X			
Hematology (CBC only)		X	X[10]	X	X	X	X	X	X			
INR/aPTT		X[10]										
Serum Chemistry		X	X[10]			X		X	X			
Urinalysis		X										

12-lead ECG		X	X[11]			X[11]		X[12]	X			
Blood sample for biomarkers[13]		X						X[13]	X			
Blood sample for pharmacokinetic analysis			X[14]			X[14]		X[15]				
Tumor Assessment (RECIST v1.1) Chest, abdomen, pelvis CTs or MRIs.[16]		X						X[16]	X[16]		X[16]	X[16]
CA-125 measurement in case of peritoneal disease and previously diagnosed ovarian cancer		X										
HRQoL[17]		X						X[17]			X[17]	X[17]
Niraparib capsules dispensed/collected or Physician's choice treatment[18]			X			X		X	X[19]			
Sample collection (whole blood) for mutational profile testing[20]		X[20]							X[20]			
Additional tests to confirm the diagnosis of MDS/AML[21]									X[21]			X[21]
Anti-cancer therapies assessment												X[22]
Survival Assessment												X[22]

[1] Treatment cycles are 21 days (3 weeks) long, visits on Day 1 of each cycle, unless otherwise specified (A 28-day cycle regimen may apply to the intravenous administration of physician's choice vinorelbine)
[2] Visits continue every 3 weeks until study medication termination visit.
[3] Centralized germline *BRCA* mutation (*gBRCA*mut) testing of DNA. Patient blood sample may be drawn and performed at any time prior to randomization. Enrollment will be based on either central or local positive for germline *BRCA* mutation result.
[4] A second blood sample will be archived for test bridging.
[5] Formalin-fixed, paraffin-embedded tumor samples (primary or metastatic site; tumor blocks or 20 slides of 5 micron thickness). Genetic and non-genetic markers relating to DNA repair will be tested (alternatively can be done after randomization or during cycle 1).
[6] A fresh tumor biopsy (FFPE and snap frozen cores) may be performed at screening and one time at progression using separate informed consent. Genetic and non-genetic markers relating to DNA repair and/or markers that predict efficacy and safety of PARP inhibitors will be tested.
[7] Negative serum pregnancy test required within 72 hours prior to the first dose of study medication for females of childbearing potential. *Pregnancy test will occur per site processes; please refer to the niraparib Investigator's Brochure for guidance.*
[8] Randomization should occur within 72 hours prior to first dose (Cycle 1, Day 1). Note that physician's choice treatment must be designated prior to randomization.
[9] Height obtained at screening only.
[10] If screening laboratory testing [hematology (CBC plus INR and aPTT), chemistry] was performed within 72 hours of Cycle 1, Day 1, repeat testing not required. Please note that during the first month of study treatment, it is mandatory to perform weekly blood draws for CBC for both treatment arms. INR and a PTT will be done only at screening. Also in case of a dose modification due to hematologic toxicity, weekly blood draws for CBC will be required for an additional 4 weeks after the adverse event has been resolved to baseline or grade 1, after which monitoring every 3 weeks may resume.
[11] For the niraparib arm only :12-lead ECG conducted, Cycle 1, Day 1 (predose and 2 hours post dose), Cycle 2, Day 1 (predose and 2 hours postdose), and cycle 1 and Cycle 2 Day 1 assessments should be conducted prior to blood draws for PK assessments.
[12] 12-lead ECG as clinically indicated in subsequent cycles.
[13] Blood samples will be taken at screening, at 6 weeks (Cycle 3/Day1) and at treatment termination (due to progression or due to any other cause). Analysis of circulating genetic and non-genetic markers relating to DNA repair and/or markers that predict efficacy and safety of PARP inhibitors will be tested.
[14] Blood samples for measurement of plasma levels of niraparib collected on Cycle 1, Day 1 and Cycle 2, Day 1 predose (within 30 minutes) and 2 hours post dose.
[15] Additional blood samples for plasma levels of niraparib collected on Cycle 4, Day 1 predose (within 30 minutes).

[16] Chest, abdomen and pelvis CT or MRI as well as CTs or MRIs scans of any other known sites of the disease are required at screening; thereafter every 6 weeks ±7 days (i.e. every 2 cycles) for the first 12 months, then every 9 weeks ±7 days (i.e. every 3 cycles) until disease progression. Tumor assessments must continue on schedule if patients have dose delays.
If the patient discontinues prior to disease progression, tumor imaging will continue at specified time intervals (every 6 weeks ± 7 days during the first 12 months after randomization, and then every 9 weeks ± 7 days weeks) until progression or until the start of subsequent anti-cancer therapy.
Patients without measurable disease at baseline are not excluded from this study. These patients should be followed with the same assessment schedule as those with measurable disease at baseline and throughout the study.
[17] Questionnaires include EORTC QLQ-C30 and EQ-5D-5L (protocol, Appendix F and Appendix I). The time schedule is detailed in the protocol, Section 10.4.1. The questionnaires must be filled within 4 weeks before randomization and subsequent questionnaires are filled in every 2 cycles (i.e., every 6 weeks ±7 days) for the first 12 months while on-treatment and every 3 months after study medication discontinuation. HRQoL forms will be collected regardless of progression status and will be limited to the first 12 months after randomization.
[18] Physician's choice chemotherapy (eribulin, vinorelbine, gemcitabine, or capecitabine) to be administered according to product package insert or local standard of care. Gemcitabine will be administered as single agent as per NCCN guidelines. In France gemcitabine is not allowed to be chosen as a treatment in the physician's choice arm.
[19] No new study medication dispensed.
[20] Blood samples collected at screening and EOT (due to any cause including development of new MDS/AML) will be stored for evaluation if necessary for assessing niraparib-related risk for MDS/AML development (e.g if the patient develops MDS/AML during treatment or post- treatment follow- up). Mutation profile before and after study treatment will be compared to determine whether any mutations were present prior to study treatment. Additional details on sample collection and analysis can be found in protocol Section 12.3.5.
[21] For a highly clinically suspected MDS/AML case reported while a patient is receiving treatment with the study drug or being followed for post- treatment assessments; the patient should be referred to the local hematologist to confirm the diagnosis of MDS/AML. Results of any additional tests performed by the hematologist should be reported as well in the e- CRF. Testing with bone marrow aspirate and biopsy is strongly recommended in these cases. The study site must receive a copy of the hematologist's report of aspirate/ biopsy findings which must include a classification according to World Health Organization (WHO) . A whole blood sample will be also collected for mutational profile testing for any highly clinically suspected MDS/AML case reported during treatment.
[22] Assessments to occur every 3 months following study medication discontinuation. In addition to survival, this assessment includes outcomes for subsequent anticancer therapies including any new malignancy information.
[23] From registration. Registration must be done directly after informed consent signature by the patient

2.2. Sample Size

At least 306 g*BRCA*$_{mut}$ patients, confirmed by the centralized test, will need to be randomized.

The overall sample size for this study is based on the overall survival endpoint and is determined based on the alternative hypotheses that niraparib will result in an improvement of 4 months in median survival of 9 to 13 months (corresponding to a hazard ratio = 0.69). For a true hazard ratio of 0.69, 265 deaths will provide 80% power (1-sided alpha = 0.025). Assuming 10 patients eligible for the primary analysis population for efficacy are enrolled per month in, with 306 patients, 265 deaths are expected to occur approximately 54 months after the first patient enrolled.

Assuming 40% of patients will be randomized on the basis of a local *BRCA* test and assuming that 15% of those patients will not be *BRCA* mutated per central test, it is estimated that an over-enrollment by 18 patients is needed to obtain the required 306 patients in the analysis population. The final PFS analysis is planned after 137 PFS events have occurred or end of recruitment, whichever occurs later. With 137 PFS events, there is 80% power (1- sided alpha=0.025) to detect an HR 0.6 (equivalent to 3 to 5 months).

2.3. Randomization and Stratification

Patients will be centrally randomized in a 2:1 ratio (treatment: physician's choice). Permuted block randomization will be used for random treatment allocation stratifying by visceral disease (yes vs no), histology (TNBC vs ER/PR positive) and number of lines of prior cytotoxic chemotherapy (not including hormonal therapy) for advanced/metastatic disease (0-1 or 2).

3. STUDY OBJECTIVES

3.1. Primary Objective

The primary objective of this study is to compare progression-free survival (PFS), as assessed by blinded central review, of patients with advanced/metastatic HER2-negative *gBRCA*mut breast cancer when treated with niraparib as compared to those treated with physician's choice single agent chemotherapy standards (eribulin, vinorelbine, gemcitabine or capecitabine).

3.2. Secondary Objectives

3.2.1. Key Secondary Objective

To compare overall survival (OS) of patients with advanced/metastatic HER2-negative *gBRCA*mut breast cancer when treated with niraparib as compared to those treated with physician's choice single agent chemotherapy standards (eribulin, vinorelbine, gemcitabine or capecitabine)

3.2.2. Other Secondary Objectives

- To establish germline *BRCA* mutation status of screened patients using a centrally provided, validated test as well as future tests, and determine concordance between tests for the purpose of developing a commercial companion diagnostic test
- To evaluate safety and tolerability as measured by all AEs
- To compare PFS using investigator assessment of progression
- To evaluate time to treatment failure (discontinuation of treatment for any reason)
- To compare response rate and duration of response
- To compare time to deterioration of health-related quality of life (HRQoL): European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and EuroQol 5 Dimension 5 Level (EQ-5D-5L)
- To describe subsequent therapies and potential relationships with outcomes
- To assess genetic and non-genetic biomarkers relating to treatment efficacy. Germline and tumor mutations may be explored including somatic *BRCA*1 and 2 mutations, reversion mutations, loss of heterozygosity as well as genome landscape and transcriptional or functional measures of homologous recombination (HR) deficiency.
- To assess outcomes by germline mutation *BRCA*1 vs *BRCA*2
- Descriptive summary statistics will be used to summarize post- treatment data (i.e subsequent anticancer therapies and any new malignancy).

4. STUDY ENDPOINTS AND EVALUATION

4.1. Efficacy Endpoints

4.1.1. Primary Efficacy Endpoints

PFS per blinded central review, defined as the time from randomization to the earliest date of death or disease progression (PD).

4.1.2. Key Secondary Efficacy Endpoints

Overall survival (OS), defined as the time from randomization to the date of death of any causes.

4.1.2.1. Other Secondary Efficacy Endpoints

- Progression-free survival (PFS) using investigator assessment of progression, defined as the time from randomization to the earliest date of death or date of disease progression (PD) as reported by investigator.
- Overall response rate (ORR), defined as percentage of patients who achieved CR or PR to treatment evaluated using RECIST v1.1
- Duration of response (DOR), defined from the time measurement criteria for CR or PR (whichever is first recorded) are first met until the first date that recurrent or progressive disease is objectively documented.
- Time to treatment failure (TTF), defined as the date of randomization to discontinuation of treatment for any reason, including but not restricted to disease progression, treatment toxicity and death.

4.2. Safety Evaluations

- Treatment emergent adverse events (TEAEs)
- Clinical laboratory assessment
  - Hematology (CBC only)
  - Biochemistry
  - Urinalysis at baseline
  - Serum pregnancy testing at baseline
- Physical examination findings
- Vital signs including weight
- ECOG performance status
- ECG findings

4.3. Demographics and Baseline Characteristics

- Demographics and baseline characteristics
- Medical history

  - Medical history
  - History of myelosuppression
- Disease history
  - Initial diagnosis and primary/adjuvant treatment
  - Treatment of the current breast cancer in the metastatic setting
  - Ovarian cancer
  - Other invasive malignancies
- Previous and concomitant medications

4.3.1. Pharmacokinetics Evaluations

Blood samples for measurements of plasma levels of niraparib will be obtained in the experimental arm on cycle 1/ day 1 and on cycle 2/ day 1 at the following timepoints: 0 (pre-dose within 30 minutes) and 2 hours post dose. In subsequent cycles, a blood sample for measurements of plasma levels of niraparib will be obtained on cycle 4/ day 1 pre-dose (within 30 minutes) only.

The plasma concentration-time data is analyzed by non-compartmental analysis using WinNonlin version 6.2.1 or higher.

PK evaluations include:

- Plasma concentrations
- Pharmacokinetic parameters

A PK analysis was not conducted and will not be described in a separate analysis plan.

4.4. Quality of Life Assessment

Health related quality of life (HRQoL) is used to evaluate patients' quality of life associated with the medical strategies on cancer treatment.

Patients' life quality evaluation includes:

- Time to deterioration of health-related quality of life assessed by QLQ-C30
- Time to deterioration of health-related quality of life assessed by EQ-5D-5L

Here, time is defined as the time of randomization to the first observed events of death, progression, or deterioration. An HRQoL analysis was not conducted and will be not addressed in a separate analysis plan.

4.5. Translational Research

The translational research evaluations include:

- Concordance between g*BRCA*$_{mut}$ tests
- Subsequent therapies and potential relationships with outcomes
- Genetic and non-genetic biomarkers relating to treatment efficacy

- Outcomes by germline mutation *BRCA*1 vs *BRCA*2

A translational research analysis was not conducted and will not be described in a separate analysis plan.

5. DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

5.1. Definition of Baseline

For all evaluations unless otherwise noted, baseline is defined as the most recent non-missing measurement prior to or on the first administration of study drug. Baseline can be the same date as first dose, given the measurement is expected prior to first dose when only date information is available.

5.2. Definition of Treatment Period

Treatment period is defined as the time from the first dose of study treatment through 30 days after last dose of study treatment.

5.3. Definition of Relative Study Days

Unless otherwise noted, relative study days (Rel Days) of an evaluation are defined as number of days relative to the first dose date of study drug which is designated as Day 1, and the preceding day is Day -1, the day before that is Day -2, etc. Relative study days are calculated as an evaluation date minus first dose date of study drug, and plus 1 day if evaluation date is on or after first dose date.

Relative study days take negative values if evaluation date occurs prior to first dose date and take positive values if evaluation date occurs on or after first dose date of study drug.

5.4. Analysis Visit Window

5.4.1. Safety Analysis Visit Window

For safety parameters as described in Section 4.2, measurements collected from unscheduled visits will not be included in the by-visit summary tables but will be included in the listings. Early termination visits for safety measurements will not be mapped to any scheduled post-baseline visit but will be used as the last assessment during treatment period.

5.4.2. Efficacy Analysis Visit Window

For efficacy assessment, all records including unscheduled visit will be included in the analysis.

5.5. Safety Data Handling

For all safety data, only observed data will be used for analyses, and missing data will not be imputed.

5.5.1. Handling of Repeated Clinical Laboratory Tests

For repeated tests, the highest or lowest laboratory result reported at the visit will be recorded in the summary table.. Lab results beyond the detectable limits will be reported as detectable limits for calculating descriptive statistics.

All the laboratory test results will be included in the data listings as reported.

5.5.2. Handling of Partial Dates for Adverse Events

When determining the treatment emergent AE, partial dates will be handled as follows.

- If the day of the month is missing, the onset day will be set to the first day of the month unless it is the same month and year as first dose date. In this case, the onset date will be assumed to be the first date of treatment.
- If the onset day and month are both missing, the day and month will be assumed to be January 1, unless the event occurred in the same year as the study treatment. In this case, the event onset will be coded to the day of treatment to conservatively report the event as treatment-emergent.
- A missing onset date will be coded as the day of treatment. If the resulting onset date is after a reported date of resolution, the onset date will be set equal to the date of resolution.
- Imputation of partial dates is used only to determine whether an event is treatment-emergent; data listings will present the partial date as recorded in the eCRF.

5.5.3. Handling of Partial Dates for Medications

When determining prior or concomitant medications, partial start dates of prior and concomitant medications will be assumed to be the earliest possible date consistent with the partial date. Partial stop dates of prior and concomitant medications will be assumed to be the latest possible date consistent with the partial date. In the case of completely missing stop date, medication will be assumed to be ongoing. In the case of complete missing start date, medication will be assumed to be prior medication.

6. PLANNED ANALYSIS

6.1. Changes from Planned Analyses in the Protocol

Changes from planned analyses described in the Protocol are as follows:

- The per protocol patient population and derived analyses (sensitivity and efficacy) were eliminated
- Results from analyses of PK evaluations, PROs, and translational research will not be reported.
- Predefined incidence and thresholds of marked abnormalities for specific safety parameters such as clinical laboratory parameters, vital signs, and ECGs will not be reported
- Descriptive statistics for the individual single-agent therapies (eribulin, vinorelbine, gemcitabine or capecitabine) comprising the physician's choice arm will not be reported.

6.2. Interim Analysis

There will be interim analysis for futility for PFS per central review and for overall survival which will be performed using the centrally confirmed intent to treat (ITT) population.

Interim analysis for futility for PFS per central review will be done based on an estimate of when the required 93 events will be reached. A gamma family beta-spending function with a non-binding gamma (γ=-5) stopping boundary based on the actual number of PFS events at the time of interim analysis data cutoff and the minimum total target number of events of 137 will be used for the interim futility analysis of PFS, i.e. the information fraction for futility analysis is equal to the number of events observed at the interim analysis divided by 137. The futility boundary will be assessed by the EAST 6 software.

The interim analysis for overall survival will be performed using the locked database for the final analysis report. The analysis will utilize O'Brien-Fleming type boundaries derived from the Lan DeMets alpha spending function based on the actual number of events observed at the time of the interim analysis.

6.3. Final Analyses and Reporting

All final planned analyses per protocol and this SAP will be performed only after database lock.

7. ANALYSIS POPULATION AND APPLICATION

7.1. Screening Population

The Screening Population includes all screened and registered patients who sign an informed consent form and will be used for the patient disposition, protocol deviation, and inclusion or exclusion analysis.

7.2. Centrally Confirmed ITT Population

The Centrally Confirmed ITT Population includes all randomized patients with centrally confirmed germline g*BRCA* mutation. The Centrally Confirmed ITT population is the primary analysis population for all efficacy analyses. Analyses involving the ITT population will group patients by the randomized treatment arm, which does not necessarily correspond to the treatment they received.

7.3. Full ITT Population

The Full ITT population includes all randomized patients. Analyses involving the ITT Population will group patients by the randomized treatment arm, which does not necessarily correspond to the treatment they received.

7.4. Safety Population

The Safety population (SP) includes all patients who started their allocated treatment (receive at least one dose of allocated drug). The SP will be the primary analysis population for the safety analyses. Analyses involving the SP population will group patients by the treatment they actually received.

7.5. Analysis Populations Application

Unless otherwise noted, the analysis populations that will be used for creating the summary table(s) and listings of each type is provided in Table 2.

Table 2: Application of Populations on Tables, Listings, and Figures

Type	Screening	Safety	Centrally confirmed ITT	Full ITT
Enrollment	X	X	X	X
Disposition		X	X	
Protocol deviations			X	
Demographics and baseline characteristics		X	X	
Medical history			X	
Disease history			X	
Prior and concomitant medications		X		
Safety evaluations		X		
Treatment exposure		X		
Efficacy analysis			X	
Sensitivity analysis for PFS			X	

8. STATISTICAL CONSIDERATION

All summaries and statistical analysis will be performed by SAS v9.3 or later.

8.1. General Statistical Procedures

Frequency distributions for categorical variables will be provided as number of patients with a response in the category and the percentages of the total number of patients in that column. Percentages will be based on number of patients in the given population as noted. Percentages will be reported to one decimal place.

A 2-sided 95% confidence interval (CI) for categorical variables without multiplicity adjustment will be provided where appropriate for efficacy analysis. When comparison of test is required, p-value will be reported as < 0.001 if it is smaller 0.001, otherwise it will be report to 3 decimal places.

The descriptive statistics for continuous variables will be number of patients, mean, standard deviation (STD), median, minimum and maximum. Mean and median will be reported to 1 more decimal place than the raw data, while the STD will be reported to 2 more decimal places than the raw data. Minimum and maximum will be reported the same as the original data.

Time-to-event analyses will be performed using Kaplan-Meier methods and a Cox proportional hazard model.

If stated, relative study day (Rel days) which is defined as number of days relative to the first dose date of study drug (see Section 5.3 for details) will be included in the data listing.

In general, all listings will be ordered by patient ID, treatment arm and visit for available data unless otherwise specified in the text.

Safety and efficacy analysis visit windows, safety data handling (repeated laboratory tests, partial dates of AEs and medications) are described in Section 5.4 and Section 5.5.

8.2. Enrollment and Disposition

8.2.1. Patients Enrollment

Patients enrollment will be summarized for each treatment arm. The number of patients in each analysis population will be presented by treatment arm and overall.

Enrollment information will be provided in a data listing.

8.2.2. Patients Disposition

Study status including primary reasons for discontinuation from treatment will be tabulated using frequency distribution by treatment arm.

Discontinued patients from treatment will be provided in a data listing.

8.3. Protocol Deviations

Important or significant protocol deviations (PDVs) will be assessed by sponsor personnel following Protocol Deviation Guideline outlined in Clinical Management Plan.

A PDV is classified as important if there is the potential to impact the completeness, accuracy, and/or reliability of the study data, or affect a patient's rights, safety, or well-being. An important PDV is subclassified as significant if it is confirmed to adversely impact the completeness, accuracy, and/or reliability of the study data, or affect a patient's rights, safety, or well-being. All PDVs will be identified and finalized prior to database lock and documented.

Number and percentage of patients with a significant or important PDV will be tabulated by type of deviation.

All protocol deviations will be listed.

8.4. Demographics and Baseline Characteristics

8.4.1. Patients Demographics and Baseline Characteristics

Demographic and baseline (see Section 5.1 for definition) characteristics will be tabulated using descriptive statistics by treatment arm. The following variables will be included in the tables:

- The demographic data are:
  - Age at screening (years)
  - Age at randomization and category (years) and in categories 18-64, 65-74, ≥ 65, ≥ 75
  - Sex
  - Race
  - Ethnicity
- Baseline characteristics include:
  - Height (cm)
  - Weight (kg)
  - body mass index (BMI) (BMI kg/m^2, calculated as weight (kg) / height $(m)^2$)
  - ECOG performance status
  - Previous BRCA mutation
  - Central BRCA mutation (positive, BRCA1+ only, BRCA2+ only, rearrangement only, BRCA1 & BRCA2, BRCA1+ & rearrangement, BRCA2+ & rearrangement)
  - Estrogen receptor (ER) status
  - Progesterone receptor (PR) status
  - HER2 status
  - Hormone receptor (HR) status
  - Presence of bone metastases
  - Presence of brain metastases

  - Visceral disease
  - Histology
  - Number of lines of prior cytotoxic chemotherapy (not including hormonal therapy) for advanced/metastatic disease (0, 1-2, or >2)

Conversions for height and weight are as follows:

Weight (kg) = Weight (lb) x 0.4536

Height (m) = Height (cm) x 0.1

Demographics and baseline characteristics will be listed.

8.4.2. Medical History

The medical history will be coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA) dictionary. The frequency count and percentage of patients experiencing any medical conditions will be tabulated by system organ classifications (SOC) and preferred term (PT) of MedDRA for each treatment arm.

Prior myelosuppression history will be summarized using frequency distribution for each treatment arm.

A data listing of medical history and disease history will be provided.

8.4.3. Disease History

Disease history will be tabulated using descriptive data by treatment arm for the following parts.

Summary of initial diagnosis and primary/adjuvant treatment of the current breast cancer:

- Time from first diagnosis to date of randomization (months)
- Tumor stage at initial diagnosis
- T status at initial diagnosis
- N status at initial diagnosis
- M status at initial diagnosis
- Histology at initial diagnosis
- Grade at initial diagnosis
- Additional biopsy performed for metastatic/recurrent disease
  - Histology after biopsy
  - Grade after biopsy
- Surgery performed for primary tumor
- (Neo-)adjuvant therapy received
- (Neo-)adjuvant endocrine therapy received

- (Neo-)adjuvant radiotherapy received
- Number of chemotherapy regimens in metastatic setting
- Total duration of chemotherapy in metastatic setting
- Endocrine therapy regimens in metastatic setting
- Any radiotherapy given in metastatic setting
- Other systemic therapy in metastatic setting
- Prior platinum treatment
- Prior diagnosis of malignancy other than breast/ovarian cancer
- Prior diagnosis of ovarian cancer

8.4.4. Prior and Concomitant Medications

All medications as documented by the Investigator will be coded using Anatomical Therapeutic Chemical (ATC) classification based on the World Health Organization (WHO) Drug Dictionary (WHO-DD Sept 2016).

The count and percentage of patients who took prior and concomitant medications will be provided WHO Drug ATC level 3 and preferred term (PT) for each treatment arm. For the summary tables, if a patient has taken a prior or concomitant medication more than once, the patient will be counted only once for the medication.

Prior medications are defined as any medications, other than study treatment, medications for cancer treatment and pre-medications for study treatment, which ended prior to the first dose date of study treatment.

Concomitant medications are medications other than study treatments, being taken on or after the initial study treatment dosing date through 30 days after the last dose or until the start of subsequent antitumor therapy.

The use of prior medications, that includes prior anticancer regimens and concomitant medications will be provided in a by-patient data listing.

8.5. Efficacy Analysis

RECIST v1.1 will be used by central review as the primary measure for assessment of tumor response, date of disease progression. Tumor response will be assessed every 6 weeks ±7 days (i.e. every 2 cycles) for the first 12 months, then every 9 weeks ±7 days (i.e. every 3 cycles) until disease progression.

Primary efficacy analysis for PFS per central review will be evaluated using stratified log-rank test. Kaplan-Meier estimates for PFS and OS with the corresponding 2-sided 95% confidence intervals will be presented. A non-stratified log-rank test will also be performed to assess the robustness of the primary result.

In addition, Cox proportional hazards model with a term for treatment arm will be used to estimate the treatment hazard ratio and its 2-sided 95% confidence interval.

Assessment at unscheduled visit will also be included in the analysis (see Section 5.4.2).

8.5.1. Primary Efficacy Endpoint Analysis

8.5.1.1. PFS per Central Review

The primary efficacy analysis is to compare the progression free survival (PFS) per central review between niraparib treatment arm and physician's choice arm.

A log-rank test stratified on randomization factors (see Section 8.4.1 for definition) will be used to assess the difference of PFS between two arms at 1-sided α-level of 0.025 for the following hypothesis:

H_0: $PFS(t)_{\text{physician's choice}} = PFS(t)_{\text{niraparib}}$
H_a: $PFS(t)_{\text{physician's choice}} < PFS(t)_{\text{niraparib}}$

where PFS(t) represents the PFS function at any time (t).

The PFS per central review is defined as the time from randomization to the earliest date of disease progression (PD) or the date of death. PFS in months will be calculated as:

(Earlier date of PD or death – Date of randomization + 1) / 30.4375.

If the patient did not experience an event, patient will be censored. The detailed censoring and event rules according to FDA guidance on *Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics* are described in Table 3.

Table 3: Censoring Rules for PFS Per Central Review

Condition	Date of event /censoring	Censoring	Event
No baseline radiologic tumor assessments	Date of randomization	Yes	No
Documented Progression	Date of radiologic tumor assessment showing disease progression	No	Yes
No documented progression, no death	Date of last documented central tumor assessment Date of randomization if only baseline radiologic tumor assessments are available,	Yes	No
Treatment discontinuation for undocumented progression, or toxicity, or any other reason (apart from documented progression)	Date of last documented central radiologic tumor assessment	Yes	No
New anticancer treatment started	Date of last documented radiologic tumor assessment before initiation of new anti-cancer treatment	Yes	No
Death before first PD assessment	Date of death	No	Yes
Death in between 2 adequate assessment visits *	Date of death	No	Yes
Death or progression after more than 1 missed adequate assessment visit *	Date of last documented central radiologic tumor assessment before the missed visits	Yes	No

* Adequate on-protocol imaging requires an assessment every 6 week (± 7 days) for the first 12 months, and then every 9 weeks (± 7 days) thereafter, from start of study treatment until progression or start of subsequent anticancer treatment.

8.5.1.2. Sensitivity Analyses

The following sensitivity analysis will be performed to assess the robustness of the primary result:

- Repeat the same for Centrally Confirmed ITT Population
- Perform non-stratified log-rank test
- Perform univariate Cox model (non-stratified) adjusting for potential prognostic factors and potential imbalances therein
  - Niraparib treatment
  - Age (55-70, >70) using age < 55 as reference group
  - ECOG performance status (1-2) using ECOG=0 as reference group
  - Visceral disease (yes, no) as NO as reference group
  - Histology (ductal, lobular, other) using ductal Other as reference group
  - Number of lines of prior cytotoxic chemotherapy (not including hormonal therapy) for advanced/metastatic disease (0 vs. 1-2) using 0 as reference group
  - Prior platinum treatment (no vs yes) using NO as reference group
  - Germline mutation (BRCA-1 only, BRCA-2 only) using both as reference group

Cases with missing values for 1 of the above factors are excluded from the model when the factor is included in multivariate Cox model.

Hazard ratio with 95% 2-sided Wald CI will be reported for each factor in univariate and final multivariate Cox model.

8.5.1.3. Homogeneity of Results across Subgroups

Subgroup analyses will be performed for the following baseline factors by means of Cox models (with Breslow ties) including the factor of interest and the randomized treatment if the subgroup contains at least 10% of the patients of the centrally confirmed ITT population:

- Age 55-70, >70)
- ECOG performance status (0 vs 1-2)
- Visceral disease positive
- Histology (ductal, lobular)
- Number of lines of prior cytotoxic chemotherapy (not including hormonal therapy) for advanced/metastatic disease, (1-2)
- Prior platinum treatment

The subgroup analyses will be reported as a forest plot containing the treatment effect hazard ratios and 95% 2-sided Wald CIs in each subgroup originating from the Cox model.

8.5.2. Secondary Efficacy Endpoints Analysis

8.5.2.1. Overall Survival

Overall survival (OS) is defined as the time from randomization to the date of death of any causes. If the patient did not experience an event, he/she will be censored at the last follow-up date. Analysis of OS will be examined as described in Section 8.5.1.1 for centrally confirmed population. A KM plot will be provided.

8.5.2.2. PFS Per Investigator Assessment

PFS using investigator assessment of progression is defined as the time from randomization to the earliest date of death or date of disease progression (PD) as reported by investigator.

PFS in months will be calculated as

(Earlier date of death or PD reported by investigator – First dose date + 1) / 30.4375

If the patient did not experience an event, patient will be censored. The detailed censoring and event rules according to FDA guidance on *Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics* are described in Table 4.

Table 4: Censoring Rules for PFS Per Investigator Assessment

Condition	Date of event /censoring	Censoring	Event
No baseline radiologic tumor assessments	Date of randomization	Yes	No
No documented progression, no death	Date of last documented radiologic tumor assessment In the event that only baseline radiologic tumor assessments are available, the date of randomization	Yes	No
Documented Progression	Date of radiological tumor assessment showing disease progression	No	Yes
Treatment discontinuation for undocumented progression, or Toxicity or any other reason (apart from documented progression)	Date of last documented radiologic tumor assessment	Yes	No
New anti-cancer treatment started	Date of last documented radiologic tumor assessment before initiation of new anti-cancer treatment	Yes	No
Death before first PD assessment	Date of death	No	Yes
Death in between 2 adequate assessment visits *	Date of death	No	Yes
Death or progression after more than one missed adequate assessment visits *	Date of last documented radiologic tumor assessment before the missed visits	Yes	No

* Adequate on-protocol imaging requires an assessment every 6 week (± 7 days) until Month 12 and every 9 weeks (± 7 days) thereafter, from start of protocol treatment until progression or start of subsequent anticancer treatment.

The median duration and 2-sided 95% confidence interval for the median will be provided for each treatment arm.

8.5.2.3. Best Overall Response

The best overall response to treatment (CR, PR, SD, Non-CR/Non-PD, PD, or Not Evaluable) and objective response rate (CR + PR),and disease control rate (CR + PR + SD) for each patient will be summarized by treatment arm. Response rates by prognostic factors between central review assessment and investigator review assessment will be tabulated using frequency distribution.

8.5.2.3.1. Best Overall Response when confirmation is not required

For each patient, the unconfirmed best overall response (uBOR) is defined as the best time-point overall response that are recorded from the date of randomization until the date of first documented progression/recurrence, or the date of subsequent anti-cancer therapy, or the date of study discontinuation, whichever occurs first. Comparison of overall response rate (ORR) between treatment arms will be performed using Cochran–Mantel–Haenszel (CMH) test adjusting for randomization stratification factors.

8.5.2.3.2. Best Overall Response when confirmation is required

To confirm CR or PR response, tumor imaging may be performed at the earliest 4 weeks after the first indication of response or at the next scheduled scan, whichever is clinically indicated.

Tumor imaging for confirmation of response occurred less than 4 weeks after the first indication of response of CR or PR may be used for clinical decision, but it will NOT be used for determination of BOR. Confirmed BOR of each patient will be determined per medical review according to RECIST v.1.1.

ORR is defined as percentage of patients who achieved CR or PR to treatment evaluated using RECIST v1.1. Response rate per central review and by Investigational assessment for each treatment arm will be provided with 95% exact confidence interval. Comparison of overall response rate (ORR) between treatment arms will be performed using Cochran–Mantel–Haenszel (CMH) test adjusting for randomization stratification factors. P-value will be reported.

8.5.2.4. Duration of Response

Unconfirmed DOR (uDOR) per central review is defined as the time from first CR or PR whichever comes first until the time of disease progression by RECIST v1.1 or death by any cause.

Confirmed DOR per central review is defined as the time from first documentation of response (confirmed CR or PR) until the time of first documentation of disease progression by RECIST v1.1 or death by any cause.

Bothe uDOR and confirmed DOR will be calculated only for patients who responded to the study treatment using the censoring rules specified in Table 5.

uDOR in months is defined as:

(Date of Event or Censoring – Date of first CR or PR + 1)/30.4375

Confirmed DOR in months is defined as:

(Date of Event or Censoring – Date of first confirmed CR or PR + 1)/30.4375

DOR will be summarized using the Kaplan-Meier method and be displayed graphically where appropriate. The median duration and 2-sided 95% confidence interval for the median will be provided for each treatment arm.

Table 5: Censoring Rules Used for Duration of Response Analysis

Situation	Date of Event or Censoring	Outcome
Start of subsequent anti-cancer therapy without a prior documented progression or death	Date of last evaluable radiologic tumor assessment prior to or on the date of initiation of the subsequent anti-cancer therapy	Censored
No documented radiologic progression and no subsequent anti-cancer therapy started	Date of last evaluable radiologic tumor assessment	Censored
Documented radiologic progression or death after two or more consecutive missing radiologic assessments	Date of last evaluable radiologic tumor assessment before the missed tumor assessments	Censored
Documented radiologic progression or death	Earliest date of documented radiologic progression or death	Event

8.5.2.5. Time to Treatment Failure

Time to Treatment Failure is defined as the date of randomization to discontinuation of treatment for any reason, including but not restricted to disease progression, treatment toxicity, and death.

If the patient does not experience an event, he/she will be censored at the last dose date or last tumor assessment date whichever occurs later. Patients who never started any protocol treatment will be censored at time of randomization

The median duration and 2-sided 95% confidence interval for the median will be provided for each treatment arm.

8.6. Interim Analysis

This interim analysis will be performed for futility for PFS per central review and for overall survival using centrally confirmed ITT population.

PFS by central independent review will be analyzed as specified in Section 8.5.1.1 and overall survival interim analysis will be performed as specified in Section 8.5.2.1.

8.7. Safety Analysis

8.7.1. Adverse Events

AEs will be coded using MedDRA v20.0 or later and will be classified by SOC and PT of MedDRA. Severity of AEs will be assessed by investigators according to CTCAE (v4.0).

A treatment-emergent AE (TEAE) will be defined as any new AE that begins, or any preexisting condition that worsens in severity during the treatment period. For the determination of the TEAEs during the treatment period, AEs with the greatest severity before the baseline will be used as the benchmark for the comparison of the AEs occurring within 30 days after last dose date or until the start of subsequent antitumor treatment.

AEs that have a possible or definite relationship to study drug will be defined to be related to the drug while others will be defined as "not related". Any TEAEs for which the relationship to study treatment is missing will be considered as related to study treatment. TEAEs with the closest relationship to study treatment will be used for summary.

The number and percentage of patients who experienced an AE will be summarized by treatment arm.

The following types of summaries will be provided for each study treatment:

- Overview of TEAEs
- TEAEs by SOC and PT
- TEAEs by PT in decreasing frequency
- Non-Serious TEAEs (PT >= 5%) by PT in decreasing frequency
- Drug-related TEAEs by PT in descending frequency
- Drug-related TEAEs by SOC and PT
- TEAEs by SOC, PT, and Maximum CTCAE toxicity grade
- TEAEs by SOC, PT, and Maximum CTCAE toxicity grade ≥ 3
- Drug-related TEAEs by SOC, PT and Maximum CTCAE toxicity grade
- Serious TEAEs by SOC and PT
- Drug-related serious AEs by SOC and PT
- TEAEs leading to study drug discontinuation by SOC and PT
- TEAEs leading to dose reduction or interruption by SOC and PT
- Death and primary reasons causing death

For physician's choice arm, drug-related AEs refer to all AEs considered related to the administered treatment.

If a preferred term (PT) or system organ class (SOC) was reported more than once for a patient, the patient would only be counted once in the incidence for that preferred term or system organ class.

In tabulation by severity (i.e., CTCAE toxicity grade),

- For a given PT, only the most severe PT for each patient will be included.
- For a given SOC, only the most severe SOC for each patient will be included.

Similarly, in tabulation by relationship,

- For a given PT, the highest ranked relationship to treatment for each patient will be included.
- For a given SOC, the most closely related SOC to the study drug for each patient will be included.

The following tables presented as listings will be provided:

- Deaths
- Serious AEs

All AEs will be listed.

8.7.2. Extent of Treatment Exposure

Dose modifications for physician's choice drugs will be done according to the respective product package insert or local practice. Therefore, calculated dose reductions/interruptions and dose intensities will not be reported for the physician's choice arm.

Duration of treatment will be summarized by treatment arm and each study drug for following variables:

- Number of exposure cycles started as a continuous variable
  - Number and percentage of patients treated by cycles 1 to >10
  - Duration of exposure (days)
  - Average cycle duration (weeks)
    - as a continuous variable
    - in categories: <2, 2-<2.5, 2.5-<3.5, 3.5-<4, ≥4 weeks
  - Maximum cycle duration (weeks)
    - as a continuous variable
    - in categories: <2, 2 -<2.5, 2.5-<3.5, 3.5-<4, ≥4 weeks

The cycle duration is calculated as the difference between the start dates of 2 subsequent treatment cycles.

For IV drugs, the treatment duration (in days) will be calculated as:

first dose of last cycle – date of first dose + 21 – date of randomization + 1

For oral drugs, the treatment duration (in days) will be calculated as:

last dose administration - first dose administration + 1

Dose modification and relative dose intensity for niraparib arm will include:

- Number of patients with dose reduction or interruptions combined
- Duration of exposure (days)
- Actual cumulative dose (mg), defined as sum of all doses actually administered
- Actual dose intensity (mg/day), defined as actual cumulative dose (mg) divided by the duration of exposure (days)
- Relative dose intensity (%), defined as actual dose intensity (mg/day) divided by the intended dose intensity (mg/day)
  - as a continuous variable
  - in categories: ≤70%, 70-≤90%,90-≤110%, 110-≤120%, >120%.

Details of study treatment administration and accountability will be listed by treatment arm for Safety Population.

8.7.3. Clinical Laboratory Tests

All laboratory parameters collected at each center's local laboratory will be converted from original values and units if supplied and converted to SI values and units to be classified as normal, low, or high based on normal ranges and units of measurement.

For hematology (CBC only) and serum chemistry laboratory parameters which are normalized in SI units, descriptive summary tables for observed values and changes from baseline will be provided by visit and treatment arm for Safety Population.

As the raw data lacks values to determine NCI CTCAE v4.0 toxicity grades and laboratory normal ranges, summary and change from baseline for hematology and chemistry tables will not be reported.

Separate listings will be provided for urinalysis, and pregnancy testing by visit, treatment arm and patient ID for Safety Population.

8.7.4. Physical Examination Findings

Physical examination will be listed.

8.7.5. Vital Signs

Vital signs (systolic and diastolic blood pressure (mmHg), heart rate (bmp), temperature (^{0}C), height (cm), and weight (kg) will be summarized and change from baseline by visit and treatment arm. Observed vital signs and changes from baseline will be provided for each parameter.

Conversion of temperature is as following:

Temperature (ºC) = (Temperature (ºF) – 32) x 5/9

A patient-detailed listing of vital signs (including weight) will be provided.

8.7.6. ECOG performance status

The ECOG shift from baseline toxicity grade to worst (highest) post-baseline toxicity grade during the on-treatment period (see Section 5.3 for definition) will be summarized for Safety Population.

Listings will be presented by treatment arm.

8.7.7. Electrocardiogram (ECG)

The following analyses will be performed on Safety Population for each applicable ECG parameters (Heart Rate [HR], RR, PR interval, QRS interval, QT interval, and QTcF interval) for each study treatment, during the on-treatment period (see Section 5.2 for definition). For each of continuous ECG parameters, descriptive statistics at baseline, at each post-baseline time point and changes from baseline at each post-baseline time point. If there are multiple measurements at a time point, the average of the replicate measurements should be taken at each time point.

- Frequency (number and percentage) of patients with notable ECG values according to the following categories: QTcF increase from baseline > 30 ms, > 60 ms
- QTcF > 450 ms, > 480 ms, > 500 ms
- HR ≤ 50 bpm and decrease from baseline ≥ 20 bpm
- HR ≥ 120 bpm and increase from baseline ≥ 20 bpm
- PR ≥ 220 ms and increase from baseline ≥ 20 ms
- QRS ≥ 120 ms

QTcF which is corrected QT interval is calculated using Fridericia's formula as QT/(RR).

Patients with notable ECG interval values and qualitative ECG abnormalities will be listed for each patient and time point and the corresponding notable values and abnormality findings will be included in the listings.

Unscheduled ECG measurements will not be used in computing the descriptive statistics for change from baseline at each post-baseline time point. However, they will be used in assessing the minimum and maximum of all visits and in the analysis of notable post-baseline abnormal ECG results. Listings will be presented for ECG.

8.8. Additional Data Presentation as Listing

- Subsequent anticancer treatment

APPENDIX 1. EUROPEAN ORGANIZATION FOR THE RESEARCH AND TREATMENT OF CANCER: PR-30-5010-C STATISTICAL ANALYSIS PLAN

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STATISTICAL ANALYSIS PLAN APPROVAL FORM

EORTC Study Number	1307		
EORTC protocol version and date	Version 6, 13 January 2017		
SAP version and date:	Version 1, 24 January 2017		
Purpose of the SAP [select]	Core SAP for fully supported study		
	Name	Date	Signature
EORTC Study Statistician (author)	PPD	PPD	PPD
EORTC Clinical Research Physician	PPD	PPD	PPD
TESARO representatives: - PPD - PPD	PPD PPD	24/01/2017	PPD
EORTC Head of Stat Department (or designee)	PPD	PPD	PPD

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EORTC protocol 1307
(EudraCT number 2013-000684-85)

A phase III, randomized, open-label, multicenter, controlled trial of niraparib versus physician's choice in previously treated, HER2-negative, germline BRCA mutation-positive breast cancer patients

✦ Study Coordinator:
PPD, Royal Marsden Hospital and Institute of Cancer Research, United Kingdom, Breast International Group (BIG)

Statistical Analysis Plan
Version 1.0

Date
24 01 2017

✦ prepared by:
PPD, biostatistician EORTC

✦ with the collaboration of:
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Table of Contents

1 List of abbreviations

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CCD	clinical cut-off date
CI	confidence interval
CR	complete response
CRF(s)	case report form(s)
CT	contrast-enhanced computed tomography (CT)
CTC	common terminology criteria
CTCAE	common terminology criteria for adverse events
ECG	electrocardiography
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EORTC	European Organisation for Research and Treatment of Cancer
ER	estrogen receptor
FAR	final analysis report
FDA	Food and Drug Administration
FU	follow-up
GGT	gamma glutamyltransferase
HR	hormone receptor
HRQoL	Health-related quality of life
HER-2	human epidermal growth factor receptor 2
IDMC-PFS	Independent Data Monitoring Committee report for the interim analysis for futility for PFS
IDMC-OS	IDMC report for the interim analysis for OS
INR	international normalized ratio
ITT	Intent-to-treat
IQR	interquartile range
IV	intravenous(ly)
LDH	lactate dehydrogenase
LLN	lower limit of normal
MedDRA	medical dictionary for regulatory activities
MRI	magnetic resonance imaging

MRP	medical review plan
ORR	overall response rate
OS	overall survival
OS-AR	analysis report for the final analysis of the overall survival endpoint (OS-AR)
PD	progressive disease
PT	preferred term (AE term)
aPTT	activated partial thromboplastin time
PTT	partial thromboplastin time
PR	progesterone receptor
PRO	patient-reported outcomes
PFS	progression-free survival
QD	quaque die (once daily)
QLQ-C30	quality of life questionnaire C30
QoL	quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
SAR	serious adverse reaction
SD	stable disease
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SOC	System Organ Class
SUSAR	suspected unexpected serious adverse reaction
TTQ	time to HRQoL deterioration
ULN	upper limit of normal
WBC	white blood cell

2 Background

2.1 Scope

This Statistical Analysis Plan (SAP) describes the statistical analyses that will be performed for:

- the Independent Data Monitoring Committee (IDMC) report for the interim analysis on futility for progression-free survival (IDMC-PFS)
- the final analysis report (FAR)
- the IDMC report for the interim analysis for overall survival (IDMC-OS)
- the analysis report for the final analysis of the overall survival endpoint (OS-AR)

of the intergroup European Organization for the Research and Treatment of Cancer (EORTC)-1307-BCG, BIG5-13, TESARO PR-30-5010-C protocol, titled "A phase III, randomized, open-label, multicenter, controlled trial of niraparib versus physician's choice in previously treated, HER2-negative, germline BRCA mutation-positive breast cancer patients." Section 7 provides an overview table documenting which of the analyses described in Section 6 will be performed for which report.

The reports will be prepared by the EORTC according to EORTC standard operating procedures and Policies. The FAR will include all results needed to prepare publication of the primary results. A separate SAP will be made for the translational research analyses.

The FAR and OS-AR will be programmed and prepared by the EORTC study statistician and statistical analyst (if applicable). The IDMC-PFS and IDMC-OS will be prepared and presented to the IDMC by the reporting statistician. The IDMC-PFS and IDMC-OS reports are confidential documents, the contents of which will only be accessible to the IDMC, IDMC administrator, and the EORTC reporting statistician, until the end of the trial.

The specifications detailed in the present analyses plan will supplement but never supersede the key specifications in the protocol, (namely the sections on "analysis of primary or key secondary endpoints" "analysis population" and "method"). Any change with respect to the specifications in the protocol will be explicitly mentioned and justified.

2.2 Trial design [as in protocol version 6, January 13, 2017]

This is a Phase III, randomized, two-arm, open-label, multicenter, superiority study to compare niraparib with physician's treatment choice in patients with HER2-negative *gBRCA*^{mut} breast cancer. After registration, eligible patients will be randomized 2:1 to:

Arm 1: niraparib orally at a dose of 300 mg daily (QD) on a continuous dosing regimen
Arm 2: physician's choice amongst one of the following 4 single agents (intravenous [IV] eribulin, IV or oral vinorelbine, IV gemcitabine, or oral capecitabine), according to the nationally available and approved treatment (Gemcitabine will be administered as single agent as per National Comprehensive Cancer Network [NCCN] guidelines. In France, gemcitabine is not allowed as a treatment in the physician's choice arm.)

Patients will continue on study medication until disease progression, as long as, in the investigator's opinion, they are benefitting from treatment and do not meet any other treatment discontinuation criteria.

See also the trial scheme in Figure 1.

Clinic visits will be conducted at the beginning of every cycle (ie, every 3 weeks ± 3 days). Contrast-enhanced computed tomography (CT), or magnetic resonance imaging (MRI) if CT is not feasible, will be required at screening and every 6 weeks ± 7 days for the first 12 months, then every 9 weeks ± 7 days until disease progression. Patients will continue on their assigned treatment until disease progression (determined by Response Evaluation Criteria in Solid Tumors [RECIST] v.1.1), unacceptable toxicity, death, withdrawal of consent, or they are lost to follow-up.

Evaluation of CT scans and MRI, including determination of response to treatment and date of progression based on RECIST v.1.1, will be conducted by a central blinded review committee comprised of 2 radiologists, with an arbiter as necessary. Results of the central blinded assessment will be used to determine the primary efficacy endpoint of PFS and will be conducted retrospectively. The study investigators also will assess response to treatment and date of progression, based on RECIST v.1.1, during the conduct of the study.

Patient-reported outcomes (PROs) will be evaluated at screening, during the treatment period, and after treatment discontinuation, for a maximum period of up to 12 months after randomization.

Safety will be evaluated throughout the study by AE monitoring and clinical laboratory assessments, (hematology, chemistry), vital signs, electrocardiograms (ECGs), physical examinations, and use of concomitant medications.

After treatment discontinuation, information on subsequent anticancer therapy and survival (including new malignancy information) will be collected. If the patient discontinues prior to disease progression, tumor imaging and assessment of PROs will continue during the post-treatment phase at specified time intervals until disease progression or until the patient starts his/her subsequent anticancer therapy. No crossover to niraparib is permitted following discontinuation from physician's choice treatment.

The IDMC was established to provide independent review and assessment of the efficacy and safety data in a systematic manner and to safeguard the interest and safety of patients participating in the study. The membership, key responsibilities of the IDMC, and the corresponding procedures were defined in an IDMC charter.

2.3 Sample size [as in protocol version 6, January 13, 2017]

At least 306 $gBRCA^{mut}$ patients, confirmed by the centralized test, will need to be randomized.

The primary analysis population for efficacy (including primary PFS and OS analyses) constitutes all randomized patients who have a germline BRCA mutation per central laboratory results (Myriad Genetics, Inc., USA, hereafter referred to as "Myriad")

The overall sample size for this study is based on the overall survival endpoint, and is determined based on the assumption that niraparib will result in an improvement of 4 months in median overall survival, from 9 to 13 months (corresponding to a hazard ratio= 0.69). For a true hazard ratio of 0.69, 265 deaths will provide 80% power at a 1-sided alpha of 0.025. Assuming 10 patients who are eligible for the primary analysis population for efficacy are enrolled per month, with 306 such patients, 265 deaths are expected to occur approximately 54 months after the first patient enrolled. At the time of the final PFS analysis (primary endpoint), an interim analysis will be performed on OS, using an O'Brien-Fleming alpha spending function (protocol Section 8.3).

Assuming 40% of patients will be randomized on the basis of a local BRCA test, and assuming that 15% of those patients will be BRCA-negative by the central test, it is estimated that 324 patients will need to be randomized to obtain the required 306 patients in the analysis population. If the average enrollment rate is greater than 11 patients per month during the second year of enrollment, the sample size to achieve the required 265 events may be increased up to 350 $gBRCA^{mut}$ patients in the primary efficacy analysis population.

The PFS analysis is designed to give 80% power to detect an HR 0.6 (equivalent to 3 to 5 months) with a one-sided alpha of 0.025, which will require approximately 137 PFS events to perform the final analysis. All patients should be recruited before the final PFS analysis is conducted, and therefore the final PFS analysis is to be conducted at approximately 137 events or end of recruitment, whichever occurs later. If final analysis is done by the end of enrollment, all PFS events occurred by the end of enrollment will be included in the analysis. Patients should be continued to be followed until death even after the final analysis of PFS to assess long-term effects of niraparib.

A gate-keeping strategy (i.e. sequential testing procedure) will be used to test PFS and OS. OS will be tested at a 1-sided alpha of 0.025 only if the final test on PFS is significant at a 1-sided alpha of 0.025. This is motivated by the fact that OS is defined as a key secondary endpoint and such approach allows control of the overall Type I error rate. One futility interim analysis on the primary endpoint of PFS is planned. This futility analysis will be performed after approximately 93 (68%) of the minimum required total number of PFS events have been recorded. A gamma family beta spending function with a non-binding gamma ($\gamma = -5$) stopping boundary will be used for the futility analysis.

An interim analysis of overall survival is planned at the time of the final PFS analysis. The interim analysis will utilize O'Brien-Fleming type boundaries derived from the Lan DeMets alpha spending function based on the actual number of deaths observed at the time of the interim analysis.

Overall survival (accounting for interim analysis performed at the time of final PFS analysis) and PFS (including futility analysis) sample size calculations were performed using PROC SEQDESIGN in SAS and confirmed with East software.

2.4 Objectives of the trial [as in protocol version 6, January 13, 2017]

2.4.1 Primary objective

The primary objective of this study is to compare progression-free survival (PFS), as assessed by blinded central review, of patients with advanced/metastatic HER2-negative *gBRCA*^{mut} breast cancer when treated with niraparib as compared to those treated with physician's choice single agent chemotherapy standards (eribulin, vinorelbine, gemcitabine or capecitabine).

2.4.2 Secondary objectives

2.4.2.1 Key secondary objective

To compare overall survival of patients with advanced/metastatic HER2-negative *gBRCA*^{mut} breast cancer when treated with niraparib as compared to those treated with physician's choice single agent chemotherapy standards (eribulin, vinorelbine, gemcitabine or capecitabine).

2.4.2.2 Other secondary objectives

1. To establish germline *BRCA* mutation status of screened patients using a centrally provided, validated test as well as future tests, and determine concordance between tests for the purpose of developing a commercial companion diagnostic test

2. To evaluate safety and tolerability as measured by all AEs.

3. To compare PFS using investigator assessment of progression

4. To evaluate time to treatment failure (discontinuation of treatment for any reason)

5. To compare response rate and duration of response

6. To compare time to deterioration of health-related quality of life (HRQoL): European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and EuroQol 5 Dimension 5 Level (EQ-5D-5L) (Appendices D, F, I)

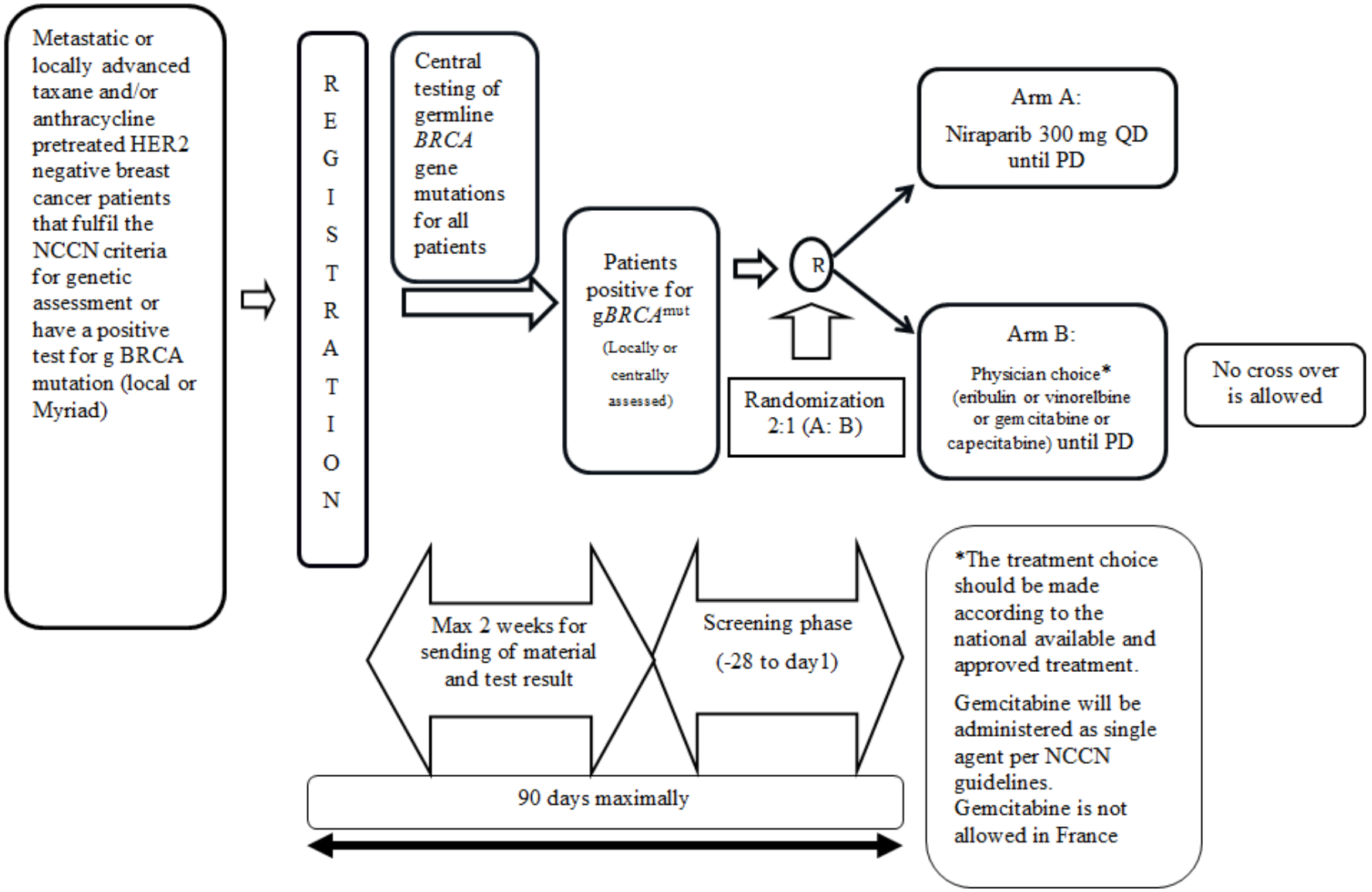
7. To describe subsequent therapies and potential relationships with outcomes

8. To assess genetic and non-genetic biomarkers relating to treatment efficacy. Germline and tumor mutations may be explored including somatic *BRCA*1 and 2 mutations, reversion mutations, loss of heterozygosity as well as genome landscape and transcriptional or functional measures of homologous recombination (HR) deficiency.

9. To assess outcomes by germline mutation *BRCA*1 vs *BRCA*2.

10. Descriptive summary statistics will be used to summarize post- treatment data (i.e subsequent anticancer therapies and any new malignancy).

Figure 1: Study Scheme



NCCN: National Comprehensive Cancer Network, QD: quaque die (once daily), PD: Progressive disease, gBRCA^{mut}, germline BRCA mutation.

3 Study conduct

Safety data will be reviewed on a regular basis by the medical review team, as documented in the medical review plan (version 1.1, June 4, 2015).

The medical review team includes EORTC representatives (clinical research physician, pharmacovigilance manager), as well as a clinical representative from the sponsor (TESARO) and the study coordinator. The medical review plan (MRP) describes the procedures and practices to be conducted by the medical team for this study, to ensure that the medical data generated from the trial are valid and reliable and that early recognition, identification, and reporting of events that affect patient safety are maintained during the trial.

Additionally, an IDMC will process a systematic, periodic review of all the safety data in the study. This process is documented in the study's IDMC charter (version 1.0, February 17, 2015). The medical review team can also request an additional IDMC review in the event that safety problems are identified for which independent advice is sought.

No outcome data is included in any of the safety reviews, apart from an overview of the secondary malignancies and deaths and their causes. See Appendix 2 for an overview of the information provided to IDMC for the safety review.

No efficacy results will be presented before the data are mature for the primary analysis according to EORTC policy 009 (version 4.2, March 3, 2015).

The FAR will contain a summary of all important amendments, a summary of the first interim analysis for futility, as well as any important issues related to the study conduct.

4 Quality assurance

The primary analysis of the FAR will undergo an independent validation by a statistician from EORTC. He/she will independently program the primary efficacy endpoint and the centrally confirmed intent-to-treat (ITT) population, based on the information provided in this SAP. The calculated variables are compared on the basis of a one-to-one comparison, and discrepancies are resolved.

The following analyses will undergo an independent EORTC validation:

- IDMC-PFS: PFS per central review assessment and the centrally confirmed ITT population
- IDMC-OS: the OS endpoint and the centrally confirmed ITT population
- OS-AR: the OS endpoint and the centrally confirmed ITT population

5 Conventions

5.1 Data Display

Unless explicitly mentioned otherwise, the following data display settings will be applied.

- Listings will always include: the patient id, the patient's institution, and the randomized treatment arm. Additional variables will be added on a case-by-case basis.
- **Frequency tables will be tabulated by the randomized treatment arm. For all categorical variables, the levels of the variables as they appear on the case report form (CRF) will be reported (with %)**. Categories with a text field specification will be tabulated as categories and then supplemented by a listing with the following information for patients fulfilling the specific condition: value of the item and text field contents).
- Delays: Dates relating to events prior to study enrollment will be presented as the delay in days (or weeks, months, or years) between the past event and the date of entry (date of randomization – date of past event + 1), and will be presented using the median, interquartile range (IQR), and range. For example, on the randomization checklist, the date of first cancer diagnosis will be presented as the time elapsed (in days, weeks, months, or years, as appropriate) since the day of the first diagnosis and the date of entry on study (date of randomization – last administration/diagnosis +1). Other delays (eg,. retreatment delays) are presented as continuous variables using the median, IQR, and range.

- Continuous variables for which a coding system exists (such as for laboratory data) will be recoded into categories (for AEs, the grading scale specified in the protocol will be used).
- Other continuous variables (for example age or dose) will be presented using the median, IQR, and range (minimum, maximum).
- If appropriate, continuous data may also be presented in categories (for example, age may also be grouped in decades).
- To convert a time interval from days to months, the interval will be divided by 30.5. To convert a time interval from days to years, the interval will be divided by 365.25.
- When the value of a variable is missing on formcrg1 or formcrg2, but is provided on formrg1 or formrg2, the corresponding data entry on the rg1 or rg2 form will be reported. For each variable, the applicable cases will be listed.
- When for some patients the value of a variable is unknown or missing, these patients will be classified in a separate category, "missing," for that variable.
- To facilitate the reading process, long listings may be included in the appendix of the FAR. They will then be referred to in the corresponding section of the FAR.

5.2 Data cleaning

- Patients who had a positive test by both Myriad (central laboratory) and another laboratory will be coded as having a BRCA mutation by Myriad on formrg2 and formcrg2.
- In the event of an unknown date, where a timeframe is known between for the event, the date in the middle of that timeframe will be entered. If the timeframe is not known, a query will be issued.

See the Conventions List for EORTC study 1307-BCG (version 1.0, May 26, 2014) for additional data cleaning conventions.

5.3 Notations in this SAP

- Variable names on the case report forms (CRFs) will be displayed in *italic*.
- The study CRFs will be referred to by either their SAS form code or the form name. See Appendix 1 for an overview of the SAS form codes and form names of the CRFs that are used in this SAP.
- Variables names containing a "-" refer to a sequence of variables, e.g., *dtsptrtn1-6* refers to *dtsptrtn1, dtsptrtn2, dtsptrtn3, dtsptrtn4, dtsptrtn5 and dtsptrtn6*.

6 Statistical analyses

6.1 Implementation of clinical cut-off date and data selection

For the IDMC-AR and the FAR, the clinical cut-off date (CCD) will be determined as the date when the number of required events is estimated to be reached, using the frequency of the events for PFS per central review.

For the OS-AR, the CCD will be determined as the date when the number of required events is estimated to be reached, on the basis of events of overall survival in the centrally confirmed ITT population.

A CCD will be applied removing forms containing patient visit data after the CCD. This will be implemented as follows:

- Screening failure form:
  The form is removed when "date of screening failure (*dtsf*) > CCD."

- The following forms are removed when the patient was randomized after the CCD:

formrg2, formcrg2, disease history form, medical history form, medical review form, initial measurements form, physical examination form at screening, myelosuppression history form.
These forms are removed when "*dor2* > CCD".

- Previous and concomitant medication form:
  The form is removed when "date of visit (*dtvisitpcm*) > CCD".

- Biochemistry form:
  The form is removed when "date of visit (*dtbio*) > CCD."

- Hematology form:
  The form is removed when "date of visit (*dthem*) > CCD."

- Follow-up measurements form:
  The form is removed when "date of visit (*dtassfm*) > CCD."

- Protocol Treatment forms:
  The form is removed when the last treatment-related date > CCD
  The last treatment-related date for formtrtc = *dtsptrtc*
  The last treatment-related date for formtrte = the maximum of *dtadme1-2*
  The last treatment-related date for formtrtg = the maximum of *dtadmg1-3*
  The last treatment-related date for formtrtn = the maximum of *dtsptrt* and *dtsptrtn1-6*
  The last treatment-related date for formtrtviv = the maximum of *dtadmv1-3*
  The last treatment-related date for formtrtvo = *dtsptrtv*

- Adverse events form:
  The form is removed when "start date (*aestdtc*) > CCD."

- End of treatment form:
  The form is removed when "date of last treatment administration (*dtlast*) > CCD."

- Follow-up form:
  The form is removed when "date of visit (*dtassfu*) > CCD," except for the survival section.
  The survival section is removed when "date last known to be alive/date of death (*dtssfu*) > CCD."

- Quality of life form:
  The form is removed when "today's date (*Q331*) > CCD."

- Health economics questionnaire:
  The form is removed when "date completed by patient (*Q527*) > CCD."

- Independent central review:
  The records in the rs dataset from the central review data export are removed when "Date/Time of Response Assessment (*RSDTC*) > CCD."

6.2 Patient availability

6.2.1 Accrual

The following information concerning accrual will be reported:

- Recruitment rate (accrual over time): A graph displaying the cumulative accrual over time and the expected accrual will be presented. A separate graph will be produced to report the number of patients registered and the number randomized in the study.
- A table with the total number of patients and percentage of patients recruited, by institution and by group, will be presented, ordered by descending volume of accrual.

6.2.2 Follow-up

The following information on the duration of follow-up (FU) in the full ITT population (Section 6.2.4) will be reported. The follow-up reporting will be repeated in the centrally confirmed ITT population (Section 6.2.4) in the appendix of the analysis report.

- FU duration by treatment arm and overall estimated by the inverse Kaplan-Meier method (Schemper & Smith, 1996): patients who died are censored on their death date (Section 6.11.1) and other patients have an event on their last follow-up date as defined below:

  The last follow-up date is calculated as the maximum of the following dates (if available):

  - End of treatment form: date of last treatment administration (*dtlast*), date last known to be alive/death (*dtssof*)
  - Follow-up form: date of visit (*dtassfu*), date last known to be alive/death (*dtssfu*)
  - Follow-up measurements form: date of visit (*dtassfm*)
  - Initial measurements form: date of visit (*dtassim*)
  - Treatment forms: last treatment-related date (Section 6.1)
  - AE forms: start date of event (*aestdtc*), stop date of event (*aeendtc*) if available
  - ECG form: date of visit (*dtecg*) if number of ECG performed at this visit (*nrecg*) > 0
  - Biochemistry form: date of visit (*dtbio*) if analysis was performed (*nybio* =1)
  - Hematology form: date of visit (*dthem*) if analysis was performed (*nyhem* =1)
  - Physical examination form: date of physical examination (*dtpe*) if performed (*nype* =1)
  - Date of randomization (*dor2*)
  - Date of screening (*dor)*

6.2.3 Eligibility

The following information on eligibility in the full ITT population (Section 6.2.4) will be reported. The eligibility reporting will be repeated in the centrally confirmed ITT population (Section 6.2.4) in the appendix of the analysis report.

- Table with eligibility status (formDM01: *nyeligteam*) and main reason for ineligibility (formDM01 *eligr,* for *nyeligteam=0*) by randomized treatment arm, as assessed by the medical review team
- Listing of ineligible patients together with main reason for ineligibility (formDM01: *eligr, txeligr,* for patients with *nyeligteam=0*)
- Listing of patients who entered with a waiver on some eligibility criteria (formDM01: *eligr, txeligr, nyeligteam,* for patients with *nyeligdev =1*)
- Listing or table of patients with deviation(s) to some eligibility criteria that are declared as eligible by the medical review team (formDM01: *eligr, txeligr,* for patients with *nyelig =1 and nyeligteam=1*)

6.2.4 Patient populations

The following patient populations will be used in the analyses:

- Screening population: all screened/registered patients. Tables for the screening population will contain 4 columns:
  - column 1: patients who were screened, not randomized, and declared a screening failure
  - column 2: patients who were screened, not (yet) randomized, and not (yet) declared a screening failure
  - column 3: patients who were randomized to physician choice
  - column 4: patients who were randomized to niraparib.

- Centrally confirmed ITT population: all randomized patients with a centrally confirmed germline BRCA mutation. Analyses involving the ITT population will group patients by the randomized treatment arm, which does not necessarily correspond to the treatment they received.

  Patients are considered to have a centrally confirmed germline BRCA mutation when on the CENBRCA form either
  - a "Variant in BRCA 1 (*NYBRCA1CEN* = 1)" is reported which is either "Positive for a deleterious mutation" or "Genetic variant, suspected deleterious" (*INTER1CEN in* (1,2)),
  - a "Variant in BRCA 2 (*NYBRCA2CEN* = 1)" is reported which is either "Positive for a deleterious mutation" or "Genetic variant, suspected deleterious" (*INTER2CEN in* (1,2)), or
  - a "BRCA1 and/or BRCA2 rearrangement found (*BRCAREARRCEN* = 1)" is reported which is either "Positive for a deleterious mutation" or "Genetic variant, suspected deleterious" (*INTERREARRCEN* in (1,2)).

  Note that this population corresponds to the ITT population specified in the protocol, which is the primary analysis population for all efficacy analyses.

- Full ITT population: all randomized patients. Analyses involving the ITT population will group patients by the randomized treatment arm, which does not necessarily correspond to the treatment they received.

  Note that the distinction is made between full and centrally confirmed ITT population to ensure that those patients who were randomized, but were not confirmed centrally to have a germline BRCA mutation after randomization, are still accounted for in this report.

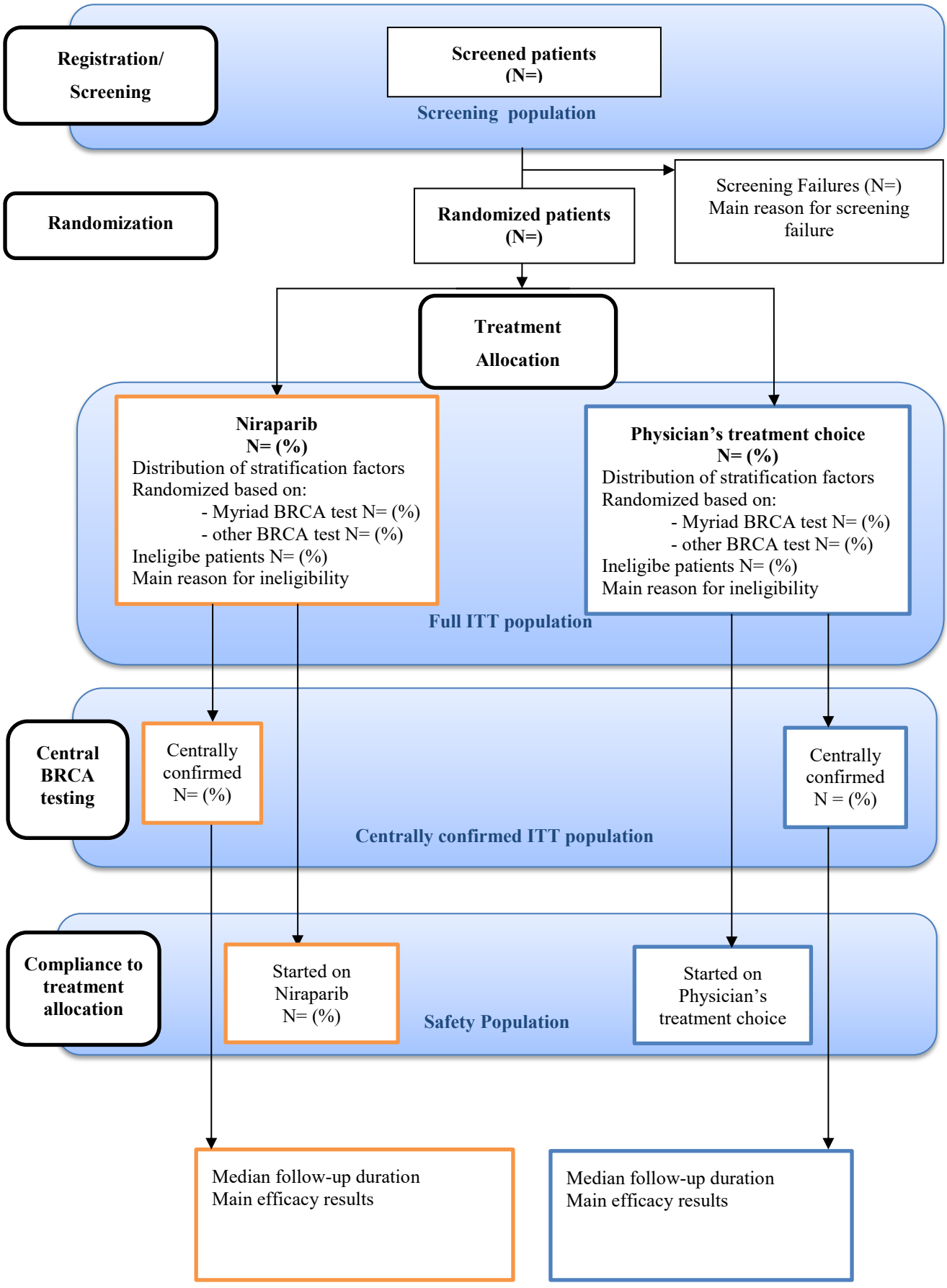
- Per-protocol population: all patients in the centrally confirmed ITT population who are eligible according to medical review (Section 6.2.3) and started on their randomized treatment (received at least 1 dose of the allocated drug). Analyses involving the per-protocol population will group patients by the randomized treatment arm, which corresponds to the treatment they actually received.

- Safety population: all randomized patients who started on their allocated treatment (received at least 1 dose of the allocated drug). Analyses involving the safety protocol population will group patients by the randomized treatment arm, which corresponds to the treatment they actually received.

A table will document the number of patients included/excluded in each of the analysis populations (by treatment arm, if applicable). Also, the main reason for exclusion from each analysis population will be documented, eg, for the full ITT population, the reason for exclusion is the main reason for screening failure (formsf: *sf1*, *txsf1*).

6.4 Study Flow Chart

The following study flow chart will be completed in the FAR.



6.5 Baseline characteristics

All baseline characteristics will be reported in the full ITT population unless explicitly specified otherwise. The baseline characteristics reporting will be repeated in the centrally confirmed ITT population, the safety population and the per protocol population in the appendix of the analysis report.

6.5.1 Baseline patient and tumor characteristics

6.5.1.1 Baseline patient and tumor characteristics at screening/registration

The following characteristics will be reported in the screening population:

- Gender (*sex*, formcrg1)
- Age at screening (median, IQR, range, by decades). *dor1* (on formcrg1) – *dob* (on patient form))
- Patient meets one of the criteria for further genetic assessment according NCCN guidelines (formcrg1: *nygenass*)
- Previously detected (prior to screening/registration) germline BRCA mutation? (formcrg1: *nyprevmut*)
- HER2 status (formcrg1: *nyhistbc*)
- Physician's choice of intended treatment for control arm (formrg1: *physchoicerg1*)

6.5.1.2 Baseline patient and tumor characteristics at randomization

- Ethnicity (formmh: *eth*)
- Race (formmh: *race*)
- Gender (*sex*, formcrg1)
- Age at randomization (median, IQR, range, by decades). *dor1* (on formcrg1) – *dob* (on patient form)
- Germline BRCA1 or BRCA2 mutation (at randomization)? (formcrg2: *nybrcamut*)
- Estrogen receptor (ER) status (formcrg2: *er*)
- Progesterone receptor (PR) status (formcrg2: *pr*)
- HER2 status (formcrg1: *nyhistbc*)
- Hormone receptor (HR) status. The HR status is calculated from the ER and PR status. It will be reported as positive when the ER status and/or the PR status is positive. It will reported as negative when both the ER and PR status are negative.
- Visceral disease? (formcrg2: *nyviscel*)
- Presence of bone metastases? (formim: *boneinvim=1, 2 or 3*)
- Presence of brain mets? (formim: *braininvim=1, 2 or 3*)
- Eastern Cooperative Oncology Group (ECOG) performance status (formph: *ecog* for *visitpe* = 0)

6.5.2 Stratification factors

- A table with the value of the stratification factors as entered at time of randomization
    - visceral disease: yes vs no (formrg2: *qval211*)
    - histology: triple negative versus ER/PR positive (formrg2: the maximum of *qval23* and *qval24*)
    - number of lines of prior cytotoxic chemotherapy for advanced/metastatic disease: 0-1 or 2 (formrg2: *qval212*)
- Listing of patients (and corresponding stratification factors) for whom there are inconsistencies between the values declared during randomization versus those updated prior to the database lock date for the report.

6.5.3 Medical history

- History of myelosuppression (formmh: *nymyh*). In the event that a patient has a history of myelosuppresion, the information on the myelosuppression history form will be listed (formmyh: *myhevent*, *myhgrade*, *dtstmyh*, *dtspmyh*, *txregimpyh*, *txtrtmyh*).

6.5.4 Disease history

Related to the initial diagnosis and primary/adjuvant treatment of the current breast cancer (per disease history form):

- Time interval between first pathological diagnosis of breast cancer and date of randomization (median, IQR, range)
- Stage at initial diagnosis (formdh: *stageinit*)
- T status at initial diagnosis (formdh: *tstage*)
- N status at initial diagnosis (formdh: *nstage*)
- M status at initial diagnosis (formdh: *mstage*)
- Histology at initial diagnosis (formdh: *thist*, *txthist*)
- Grade at initial diagnosis (formdh: *tgrad*)
- Additional biopsy performed for metastatic/recurrent disease (for patients who were M0 at diagnosis)? (formdh: *nyaddbx*) If yes, histology and grade after biopsy (formdh: *thistbx*, *txthistbx*, *tgradbx*)
- Surgery performed for primary tumor? (formdh: *nysurgproc*)
- (Neo-)adjuvant chemotherapy received? (formdh: *setadj*) If yes, the regimen, time interval between initial diagnosis and first progression (formdh: *regimadj*, *txregimadj*, *dtrecadj- dtdiag*)
- Endocrine therapy given? (formdh: *nyendoadj*) If yes, the regimen (formdh: *txendoadj*)
- Radiotherapy given? (formdh: *nyrxadj*)

Related to treatment of the current breast cancer in the metastatic setting:

- Number of chemotherapy regimens given for the current breast cancer in the metastatic setting (formdh: *nrregimmet*)

  For patients who received at least 1 regimen: the type of first regimen, the duration of treatment, and the response to this treatment (formdh: *regim1*, *txregim1*, *dtspregim1-dtstregim1*, *respregim1*)

  For patients who received at least 2 regimens: the type of second regimen, the duration of treatment, and the response to this treatment (formdh: *regim2*, *txregim2*, *dtspregim2-dtstregim2*, *respregim2*)
- Total duration of chemotherapy given for the current breast cancer in the metastatic setting (formdh: the sum of [*dtspregim2-dtstregim2]* and *[dtspregim1-dtstregim1*])
- Endocrine therapy given? (formdh: *nyendomet*) If yes, the regimen (formdh: *txendomet*)
- Radiotherapy given? (formdh: *nyrtmet*) If yes, a listing of the type (formdh: *txrtmet*)
- Other systemic therapy (not entered above)? If yes, a listing of the type, the response to this treatment, the last administration date, and the date of randomization (in the current study)

Related to ovarian cancer, for female patients only:

- Prior diagnosis of ovarian cancer? (formdh: *nypriorovdh*) If yes, stage (formdh: *stageovdh*)

Related to other invasive malignancies:

- Cancer history other than metastatic breast cancer or ovarian cancer? (formdh: *nycanchist*) If yes, a listing of the type, the date of diagnosis of the malignancy, last treatment for the malignancy (formdh: *txcanc, dtdiagcanc, dtsptrtcanc*).

6.5.4.1 BRCA testing

The following variables will be tabulated 3 times, in 3 different populations:

- the screening population

- the full ITT population
- the centrally confirmed ITT population, restricted to those patients who were randomized after a germline BRCA mutation detected at a different lab than Myriad (formcrg2: *nybrcamutnot*=2):

BRCA testing before screening:

- Previously detected germline BRCA mutation (formcrg1: *nyprevmut*)

BRCA testing before randomization:

- germline BRCA1 or BRCA 2 mutation? (formcrg2: *nybrcamutnot*)

Central BRCA testing results:

Were results from central BRCA mutation testing received? (yes, if formcenbrca is received). If yes:

- Variant in BRCA 1 or 2? (1, 2, both 1 and 2, neither 1 nor 2) (formcenbrca: *nybrca1cen* and *nybrca2cen*)
- If variant in BRCA 1 or both: specify the interpretation (formcenbrca: *inter1cen*)
- If variant in BRCA 2 or both: specify the interpretation (formcenbrca: *inter2cen*)

Previous BRCA testing results:

Was a second BRCA mutation test performed outside the context of this protocol? (yes, if formothbrca is received). If yes:

- Location of BRCA mutation test? (formothbrca: *locbrca*)
- Variant in BRCA 1 or 2? (1, 2, both 1 and 2, neither 1 nor 2) (formothbrca: *nybrca1loc* and *nybrca2loc*)
- If variant in BRCA 1 or both: specify the interpretation (formothbrca: *inter1loc*)
- If variant in BRCA 2 or both: specify the interpretation (formothbrca: *inter2loc*)

6.6 Compliance to the protocol

Compliance will be reported in the full ITT population, and repeated in the centrally confirmed ITT population in the appendix of the analysis report.

6.6.1 Central medical review of compliance to protocol

- Were there protocol treatment deviations as described in the MRP? (formdm01: *devia*) If yes, the type of violation (formdm01: *violev*)
- Were there protocol treatment deviations as described in the MRP that were judged as severe violations by the medical review team? (formdm01: *nydeviateam*) If yes, the type of violation (formdm01: *violev*)

6.6.2 Compliance to treatment allocation

Definitions:

- A patient is defined to have started on niraparib if at least 1 dose is reported on the niraparib treatment form during cycle 1 (formtrtn: max(*dosen*, *dose1n*, *dose2n, dose3n, dose4n, dose5n, dose6n*) > 0 for *cycletrn =1*)
- A patient is defined to have started on capecitabine if at least 1 dose is reported on the capecitabine treatment form during cycle 1 (formtrtc: max(*dosec*, *dose1c*, *dose2c, dose3c, dose4c, dose5c*) > 0 for *cycletrc =1*)
- A patient is defined to have started on eribulin if at least 1 dose is reported on the eribulin treatment form during cycle 1 (formtrte: max(*dosee1*, *dosee2*) > 0 for *cycletre =1*)
- A patient is defined to have started on gemcitabine if at least 1 dose is reported on the gemcitabine treatment form during cycle 1 (formtrtg: max(*doseg1*, *doseg2, doseg3*) > 0 for *cycletrg =1*)

- A patient is defined to have started on intravenous (IV) vinorelbine if at least 1 dose is reported on the IV vinorelbine treatment form during cycle 1 (formtrtviv: max(*dosev1*, *dosev2, dosev3*) > 0 for *cycletrv =1*)
- A patient is defined to have started on oral vinorelbine if at least 1 dose is reported on the oral vinorelbine treatment form during cycle 1 (formtrtvo: max(*dosev*, *dose1v, dose2v, dose3v, dose4v, dose5v*) > 0 for *cycletrvo =1*)
- A patient is defined to have started on physician's treatment choice if he/she started on capecitabine, eribulin, gemcitabine, IV vinorelbine, or oral vinorelbine.

The following information regarding treatment compliance will be reported:

- Treatment actually started (niraparib, physician's treatment choice, other, no information available) (using the definition above). If the patient did not start the allocated treatment, the reason why (formdm01: *txdevia*).
- For patients who started on another treatment or for whom no treatment information is available in the database, a listing will be provided, including any additional information concerning the treatment actually received (stored in the medical review form textboxes). (formdm01: *txdevia*, *txdmisrev*)

6.6.3 Other compliance measures

Related to the timing of the tumor measurements:

- average difference between 2 successive tumor measurement of the same patient (median, IQR, range) (formfum: *dtassfm – dtassfm[-1],* where the formfum forms are sorted by patient in ascending order on *dtassfm*, and with *dtassfm[-1]* being the previous value of *dtassfm* for the same patient)
- Histogram of the difference between 2 successive tumor measurement of the same patient (all patients, all time points). Bar width will be 3 days. (formfum: *dtassfm – dtassfm[-1]*)
- Histogram of the timing of all the tumor measurements (all patients, all time points) relative to the theoretical measurement dates as set from start of treatment (per protocol). Bar width will be 5 days. (formfum: *dtassfm* – [closest theoretical date of per protocol schedule])

Related to the assessment of the hematologic toxicity:

- Did the patient receive weekly blood tests during first month from start of treatment? (yes/no).
  Availability of a hematology form (formlbhem: *nyhem=1, dthem*) for the following 4 dates: start of treatment + 7 days (± 3 days), start of treatment + 14 (± 3 days), start of treatment + 21 (± 3 days), start of treatment + 28 (± 3 days)

- Did the patient receive weekly blood tests for 1 month following the first dose reduction for hematologic toxicity? (yes/no).
  For patients with a dose reduction due to a hematologic toxicity (investigator reported on the treatment form), availability of a hematology form (formlbhem: *nyhem=1, dthem*) for the following 4 dates: date of first dose reduction due to hematological toxicity + 7 days (± 3 days), date of first dose reduction due to hematological toxicity + 14 (± 3 days), date of first dose reduction due to hematological toxicity + 21 (± 3 days), date of first dose reduction due to hematological toxicity + 28 (± 3 days).

6.7 Exposure to treatment

The exposure will be reported in the safety population.

6.7.1 Protocol therapy

Protocol therapy consists of niraparib or physician's treatment choice among IV eribulin, IV or oral vinorelbine, IV gemcitabine, or oral capecitabine. Dose modifications for physician's choice drugs will be done according to the respective product package insert or local practice. Therefore, calculated dose reductions/interruptions and dose intensities will not be reported for the physician's choice arm.

Niraparib, capecitabine, and oral vinorelbine are oral drugs with a daily administration schedule. The cycles for these drugs were defined as 3 week time-intervals, irrespective of interruptions. The other drugs have an IV administration route, with normal cycle duration of 3 weeks. Cycle duration will be longer in the event that the next cycle needs to be delayed, eg, due to toxicity.

For IV. drugs, the treatment duration (in days) will be calculated as:

(first dose of last cycle +21 - first dose of first cycle) + 1

For oral drugs, the treatment duration (in days) will be calculated as:
(last dose administration - first dose administration) + 1

6.7.1.1 Treatment received

- The frequency of patients who received at least 1 dose of niraparib will be presented.
- The frequency of patients who received at least 1 dose of physician's treatment choice will be presented, including the type of regimen.
- A table showing the planned versus received regimen for patients randomized to the physician's treatment choice arm will be presented.

6.7.1.2 Duration of treatment

The following data will be displayed:

- Number of patients who have stopped protocol treatment and who are still on protocol treatment.
- Number of cycles of protocol therapy received (until database lock) (the maximum of: *totcyc* [formeot], *cycletrc* [formtrtc], *cycletre* [formtrte], *cycletrn* [formtrtn], *cycletrg* [formtrtg], *cycletrvo* [formtrtvo] and *cycletrv* [formtrtviv]). This will be reported separately for patients who have stopped protocol treatment and who are still on protocol treatment.
- Duration of protocol therapy (until database lock, in months) (Section 6.7.1). This will be reported separately for patients who have stopped protocol treatment and who are still on protocol treatment.

  Average cycle duration in weeks (median, IQR, range, and in categories: <2, 2 - <2.5, 2.5 - 3.5, >3.5 - 4, >4 weeks). Cycle duration calculated as the difference between the start dates of 2 subsequent treatment cycles
- Maximum cycle duration in weeks - (median, IQR, range, and in categories: <2, 2 - <2.5, 2.5 - 3.5, >3.5 - 4, >4 weeks). Cycle duration as calculated above.

6.7.1.3 Relative dose intensity for the Niraparib arm

The observed dose intensity is calculated as the total dose received divided by the duration of protocol therapy in days. For the definition of the duration of protocol therapy, see Section 6.7.1.

The relative dose intensity is calculated as the observed dose intensity (in days) divided by the theoretical dose intensity (in days), eg, for niraparib, the theoretical daily dose intensity equals 100 mg.

Relative dose intensity will be reported as median, IQR, and range, and in the following categories: ≤70%, >70-90%, >90-110%, >110-120%, >120%

6.7.1.4 Dose reductions and interruptions (calculated) for the niraparib arm

A dose reduction is defined as any dose administration of ≤ 90% of the theoretical dose for any of the protocol drugs. Dose interruptions are not reported as dose reductions, but are reported separately.

A dose interruption is defined as any dose administration of 0 for any of the protocol drugs prior to stopping protocol treatment. In the event that a dose of 0 is reported in the last cycle and there is no end treatment form available for this patient (at time of database lock), this case will count as a dose interruption and the patient is assumed to still be on treatment.

- Frequency of patients with a dose reduction of niraparib. In the event of dose reduction, the cycle and reason of first dose reduction

- Frequency of patients with a dose interruption of niraparib. In the event of an interruption, the cycle and reason of first dose interruption

6.7.2 Further anti-tumor treatment (after stop of protocol treatment)

The following variables will be reported in the group of patients who stop protocol treatment and for whom follow-up information is available for at least 2 months after stopping protocol treatment (to allow for sufficient survival/follow-up to have started a new treatment).

Additionally, the analyses will include the next line of treatment following disease progression. This will be reported in a subgroup, specifically those patients with progressive disease on protocol treatment.

- Any chemotherapy administration? (formfu: maximum of *nyctxfu*)
- Any radiotherapy? (formfu: maximum of *nyrtfu*)
- Any surgery? (formfu: maximum of *nysurgfu*)
- Any hormonal therapy? (formfu: maximum of *nyhorfu*)
- Any targeted agents? (formfu: maximum of *nytarfu*) If yes, specification of the first new targeted therapy given following the end of protocol treatment (formfu: *txtarfu*)
- Any other treatment? (formfu: maximum of *nyothfu*) If yes, specification of the first new other therapy given following the end of protocol treatment (formfu: *txothfu*)
- Niraparib given in compassionate use program? (formfu: the maximum of *nircompuse*)

The molecularly targeted treatments and other treatment might be further categorized into meaningful drug classes based on medical review.

6.8 Safety evaluations

All safety and tolerability evaluations based on the clinical database will be reported in the safety population. AE grading will be described according to CTC version 4.0.

For the reporting in this section, “during protocol treatment” is defined as:

- The Adverse Events: The time period from start of treatment up to (and including) 30 days after the last protocol treatment administration date, as reported on the end of treatment form (formeot: *dtlast*). In the event that there is no end of treatment form received at time of database lock, all AEs/laboratory results from start of treatment will be reported.
- For hematology and biochemistry: The time period from start of treatment up to the study medication termination visit (formlbhem: *visithem=1,2,3 or 4,* formlbbio: *visitbio=1 or 2*).

6.8.1 Hematology

The category “missing” means that the corresponding laboratory test was never performed during treatment. When the laboratory test was performed at least once, but the required normal ranges were not provided, this is reported as “upper limit of normal [ULN] not reported” or “lower limit of normal [LLN] not reported.”

Certain laboratory results are reported both on the hematology form and on the AE form. These variables will be reconciled during database cleaning.

- The worst grade during protocol treatment will be tabulated for the following laboratory tests/ preferred terms:

  Hematology form: white blood cell (WBC) count, neutropenia, lymphopenia, thrombocytopenia, anemia

  AE form: febrile neutropenia, anemia, neutrophil count decreased, lymphocyte count decreased, neutrophil count decreased, platelet count decreased, white blood cell decreased
- Listing of the grade ≥ 3 AEs that meet these criteria. This listing will include the baseline laboratory value and corresponding grade.

6.8.2 Biochemistry

The category "missing" means that the corresponding laboratory test was never performed during treatment. When the laboratory test was performed at least once, but the required normal ranges were not provided, this is reported as "ULN not reported" or "LLN not reported".

Certain laboratory results are reported both on the biochemistry form and on the AE form. These variables will be reconciled during database cleaning.

- The worst grade during protocol treatment will be tabulated for the following laboratory tests/ preferred terms:

  Biochemistry form: hypoalbuminemia, alkaline phosphatase, SGPT, amylase, SGOT, hyperbilirubinemia, blood urea nitrogen (BUN) abnormality, hypercalcemia, hypocalcemia, serum creatinine, gamma glutamyltransferase (GGT), hyperglycemia, hypoglycemia, hyperkalemia, hypokalemia, lactate dehydrogenase (LDH) abnormality, lymphopenia, hypermagnesemia, hypomagnesemia, hypernatremia, hyponatremia, hyperbilirubinemia.

  AE form: hypercalcemia, hyperglycemia, hyperkalemia, hypermagnesemia, hypernatremia, hypoalbuminemia, hypocalcemia, hypoglycemia, hypokalemia, hypomagnesemia, hyponatremia, serum amylase increased, GGT increased, alanine aminotransferase (ALT) increased, alkaline phosphatase (ALP) increased, aspartate aminotransferase (AST) increased, blood bilirubin increased, creatinine increased.

- Listing of the grade ≥ 3 AEs that meet these criteria. This listing will include the baseline laboratory value and corresponding grade.

6.8.3 Adverse Events

Adverse events will be tabulated by preferred term within the System Organ Class (SOC); however, for the following SOCs, AEs will be pooled across the preferred terms: Eye disorders (EYE), Hepatobiliary disorders (HEP), Immune system disorders (IMM), Injury, poisoning and procedural complications (INJ), Musculoskeletal and connective tissue disorders (MUS), Pregnancy, puerperium and perinatal conditions (PRE), Skin and subcutaneous tissue disorders (SKI), Social circumstances, Surgical and medical procedures (SUR).

The preferred term will always be included in the listings. The report will include:

- Table containing the worst grade of all reported AEs classified under the specific SOC/preferred during protocol treatment.
- Listing of all AEs during protocol treatment. The listing will include the preferred term, the date of randomization, the date of event onset, the stop date of the event, whether this event is serious, the relationship to protocol treatment, and the action that was taken with respect to the protocol treatment. This listing will be organized by the treatment received and the SOC. Within those sections, the items will be sorted by the grade and preferred term.
- Table containing the worst grade of all reported AEs classified under the specific SOC/preferred term during protocol treatment that are reported to be related or likely related to the protocol treatment.

6.8.4 Serious Adverse Events

Tables of the serious adverse events (SAEs) will be provided by the EORTC pharmacovigilance department. Unlike the data presented in other sections of the report, SAE data are based on the safety database. The safety database will be reconciled with the clinical database prior to database lock.

The following tables will be reported:

- Study safety overview per treatment arm

Randomized Treatment arm	# SAE terms	# SAR terms	# SUSAR terms	# Deaths	# Toxic deaths
Niraparib					
Physician's choice					

SAE = serious adverse event; SAR = serious adverse reaction; SUSAR = suspected, unexpected, serious adverse reaction; Toxic death = cases with at least one SAR term with fatal outcome, ie, a death judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to the study treatment. The study safety overview table lists the number of reported SAE terms, SAR terms and SUSAR terms per treatment received and the number of reported death and toxic death cases. There can be multiple reported terms within one case, but as a patient can only die once, it is the numbers of deaths and toxic death cases which are listed (instead of terms).

The column # SAE terms displays a count of all SAEs; all events which are reported as 'serious' (ie,1 seriousness criterion) regardless of relationship to the study treatment. This implies that the number of SAE terms also includes the number of SAR terms (and SUSAR, deaths, and toxic deaths terms).

The column # SAR terms displays a count of all SARs; all SAEs judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to the study treatment. This implies that the number of SARs also includes the number of SUSAR and toxic deaths terms.

The column # SUSAR terms displays a count of all SUSARs; all SARs which are considered as unexpected.

The column # Deaths displays a count of all cases with at least 1 SAE term with fatal outcome, regardless of relationship to study treatment. This implies that the number of death cases also includes the number of toxic death cases.

The column # Toxic deaths displays a count of all cases with at least one SAR term with fatal outcome, ie,. a death judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to the study treatment. *Note*, a toxic death can also be a SUSAR and vice versa, but this is not always the case.

- Suspected Unexpected Serious Adverse Reactions (SUSARs) by SOC and preferred term

Identification Number	Randomized Treatment arm	SOC	Preferred term	Count by Preferred term

- Toxic deaths by SOC and preferred term

Identification Number	Randomized Treatment arm	SOC	Preferred term	Count by Preferred term

- Line Listings of Serious Adverse Reactions (SAR)

Randomized Treatment arm	Institution identifier	Patient ID	case ID (for internal reference)	Seriousness Criteria	Reported Term (verbatim term)	Grade (CTCv4.0)	Event Start Date	Event Stop Date	Outcome	Treatment	Relationship to Treatment
Niraparib											
Physician's choice											

- Cumulative Summary Tabulation of Serious Adverse Events (SAE)

SOC	Preferred term	**Events in Niraparib arm**	**Events in Physician's choice arm**	Total number of events
Blood and lymphatic system disorders	Febrile bone marrow aplasia			
	Febrile neutropenia			
	Neutropenia			
Blood and lymphatic system disorders Total				
Gastrointestinal disorders	Abdominal pain			
	Diarrhoea			
	Nausea			
	Vomiting			
Gastrointestinal disorders Total				
…				
Grand Total				

- Cumulative Summary Tabulations of Serious Adverse Reactions (SAR)

SOC	Preferred term	**Events in Niraparib arm**	**Events in Physician's choice arm**	Total number of events
Blood and lymphatic system disorders	Febrile bone marrow aplasia			
	Febrile neutropenia			
	Neutropenia			
Blood and lymphatic system disorders Total				
…				
Grand Total				

6.9 Reasons for stopping treatment

Reasons for stopping treatment will be reported in the full ITT population. The reporting will be repeated in the centrally confirmed ITT population in the appendix of the analysis report.

- Is patient still on protocol treatment? (end of treatment form)

If not:

- Reason for stopping protocol therapy (end of treatment form)

6.10 Disease status

Disease status will be reported in the full ITT population, and entails the tabulation of the following event frequency. The reporting will be repeated in the centrally confirmed ITT population, the safety population and the per protocol population in the appendix of the analysis report.

- Disease progression, type of first event. This variable will be categorized as follows:
    1. Progressive disease (PD) both per investigator assessment and central independent review
    2. PD per investigator assessment, not confirmed by review
    3. PD per central independent review, not reported by the investigators
    4. Start of new anticancer treatment in absence of PD (by central review or investigator reported)
    5. No PD

Patients will be classified in one of these 5 categories based on their status at the time of evaluation. For the definitions of the aforementioned dates, see Section 6.11.1. When dates do not differ by more than 7 days, the corresponding events are considered to have happened instantaneously for the above classification.

For patients classified as "Start of new anticancer treatment," #4 above, the frequency of patients for whom clinical progression (not radiologically confirmed) was reported by the investigator prior to the start of new anticancer therapy, will be reported.

- Death. The patient is reported to have died if *ssof*=2 (formeot) or *ssfu*=2 (formfu); otherwise the patient is considered alive. In the event that the patient died, the main cause of death will be provided: *rdeadfof, txrdeadof* in case *ssof=2* (formeot) or *rdeadfu txrdeadfu* in case *ssfu=2* (formfu)
- Listing of early death, defined as death occurring within 90 days from randomization.
- Listing of patients who die on treatment (= up to 30 days post protocol treatment stop). Second primary malignancy. The patient is reported to have a second primary malignancy if *nynew=1* (formfu) or *dtnewof* is reported (formeot). If yes, a listing of the site/type: *txnew* in case *nynew=1* (formfu) or *txnewof* in case *dtnewof* is reported (formeot).

6.11 Statistical inference on efficacy endpoints

Efficacy analyses will be reported in the centrally confirmed ITT population, unless explicitly mentioned otherwise. The following analyses will be provided as supplementary statistics to the primary test for each efficacy endpoint. The primary test itself will be covered in the subsection for each endpoint.

- Kaplan-Meier curves by randomized treatment arm will be shown. Medians - if reached - will be presented with a 2-sided 95% confidence interval (CI) based on the nonparametric method (Brookmeyer & Crowley, 1982).
- A univariate Cox proportional hazards model with the randomized treatment as a factor and stratified by the randomization factors will be used to estimate the treatment hazard ratio and its 2-sided 95% CI. The proportional hazards assumption will be assessed by means of the graphical and numerical method based on cumulative sums of martingale-based residuals (Lin, Wei, & Ying, 1993). The method will be implemented using the 'asses' statement in the 'phreg' procedure of SAS, using the default settings. In the event that the proportional hazards assumption does not hold, how the hazard ratio changes over time will be explored by means of models involving treatment interaction with (a function of) time. The results will be displayed graphically.

6.11.1 Definitions

The following definitions for the death date, disease progression date by independent central review, and disease progression date per investigator assessment will be applied throughout the report:

- Death date
  If the patient died (according to the definition in Section 6.10), the death date is calculated as the minimum of: *dtssof* if *ssof*=2 (formeot) and *dtssfu* for follow-up forms with *ssfu*=2 (formfu); otherwise the date of death is empty.

- Disease progression date by independent central review
  The progression date is calculated from the independent central review data export, in the form rs, as the minimum of *RSDTC* for those patients for whom *RSACPTFL* = "Y" and *RSTEST*="Overall Response" and *RSORRES*="PD". If the date is missing, the patient is considered to not have a disease progression by independent central review

- Disease progression date per investigator assessment
  The progression date is calculated as the minimum of: *dtprfm* (formfum), *dtpdof* (formeot) and *dtpdradfu* (formfu). If the date is missing, the patient is considered to not have a disease progression per investigator assessment. Note that this definition implies that if the patient stops protocol treatment due to a non-radiologic (clinical) progression, this will not count as a disease progression.

- Clinical disease progression (non-radiologic) date per investigator assessment
  The clinical progression date is calculated as the minimum of: *dtcpdof* (formeot) and *dtpdclinfu* (formfu).

- Date of start of new anticancer treatment
  The minimum of *dtctxfu, dtrtfu, dtsurgfu, dthorfu, dttarfu, dtothfu* (formfu). If the date is missing, the patient is considered to not have started a new anticancer treatment.
  Any date relating to an anticancer treatment identified by medical review on the concomitant medication form will be taken into account in the calculation of this date.

6.11.2 Primary endpoint: Progression-free Survival by independent central review

This endpoint is defined as the time from randomization until the minimum of the date of death (Section 6.11.1) and the date of disease progression per independent central review. The independent central review process is documented in the Independent Review Charter (version 1.0, November 27, 2013)

For the primary analysis, PFS will be censored according to Food and Drug Administration (FDA) guidance on Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, appendix table A. The application of the guidance will be detailed below:

This endpoint considers the following as events:

- death (Section 6.10)
- disease progression per independent central review

If the patient did not experience an event, he/she will be censored. See table 1 below for more detailed censoring and event rules for this endpoint.

A documented central independent radiologic assessment is defined as the independent central radiologic review for a radiologic (CT or MRI) disease assessment, taking place before the start of the new anticancer treatment (Section 6.11.1), if applicable.

Table 1: Censoring rules for the endpoint of progression-free survival by independent central review

Condition	Date of event /censoring	Censoring	Event
No baseline tumor assessments	Date of randomization	Yes	No
Documented Progression	Date of radiological assessment showing disease progression	No	Yes
No documented progression, no death	Date of last documented central independent radiologic assessment In the event that only baseline tumor assessments are available, the date of randomization	Yes	No
Treatment discontinuation for undocumented progression, or toxicity, or any other reason (apart from documented progression)	Date of last documented central independent radiologic assessment	Yes	No
New anticancer treatment started	Date of last documented central independent radiologic assessment before initiation of new anti-cancer treatment	Yes	No
Death before first PD assessment	Date of death	No	Yes
Death in between 2 adequate assessment visits *	Date of death	No	Yes
Death or progression after more than 1 missed adequate assessment visit *	Date of last documented central independent radiologic assessment before the missed visits	Yes	No

* Adequate on-protocol imaging requires an assessment every 6 weeks (± 7 days) until Month 12, and every 9 weeks (± 7 days) thereafter, from start of protocol treatment until progression or start of subsequent anticancer treatment.

The primary test will be performed at the 1-sided 0.025 significance level. The primary PFS analysis will be performed using a stratified log-rank test for the difference in the distribution of PFS between the niraparib group and the control group (one-sided α-level of 0.025). The randomization factors will be used as the strata for this test. The following hypothesis will be tested:

H0: PFS(t)physician choice = PFS(t)niraparib

Ha: PFS(t)physician choice < PFS(t)niraparib

where PFS(t) represents the progression-free survivorship function at any time (t).

The aforementioned analysis on the primary endpoint will undergo an independent validation by an EORTC statistician. The independent EORTC statistician will independently program the analysis, based on the information provided in this SAP. The output of this analysis will be compared and discrepancies will be resolved.

Sensitivity analyses

- The analysis mentioned above will be repeated in the per protocol population, to assess the robustness of the primary result.
- The analysis mentioned above will be repeated in the full ITT population, to assess the robustness of the primary result when including patients who were not centrally confirmed to be BRCA-positive.
- A non-stratified log-rank test will also be performed to assess the robustness of the primary result.
- A multivariate Cox model will be fitted to assess the robustness of the treatment effect when adjusting for (potential) prognostic factors and (potential) imbalances therein. The Cox model (with Breslow ties) will be constructed based on a backward stepwise selection method, with a two-sided 0.10 cutoff for selection, and forcing treatment arm to stay in the model. The following factors will be considered for inclusion in the model:
    - Age (< 55,55-70,>70)
    - ECOG performance status (0 vs 1-2)
    - visceral disease (yes, no)
    - histology (ductal, lobular, other)
    - number of lines of prior cytotoxic chemotherapy (not including hormonal therapy) for advanced/metastatic disease (0, 1-2)
    - prior platinum treatment (no vs yes)
    - germline mutation (BRCA-1 vs BRCA-2 vs both)

  Cases with missing values for 1 of the above factors are excluded from the model (when the factor is included in that model).

  The reporting of this analysis will contain in 1 table:

    - the fitted univariate Cox models for each of the factors (Hazard ratio for each factor and 95% 2-sided Wald CI)
    - the fitted full multivariate Cox model (Hazard ratio for each factors and 95% 2-sided Wald CI)
    - the multivariate Cox model after model selection as described above (hazard ratio for each factor and 95% 2-sided Wald CI, Type III test p-value for each factor)

Homogeneity of results across subgroups

Subgroup analyses will be performed for the following baseline factors by means of Cox models (with Breslow ties) including the factor of interest and the randomized treatment if the subgroup contains at least 10% of the patients of the centrally confirmed ITT population:

- Age (< 55,55-70,>70)

- Race (Ashkenazi Jewish descendant, White or Caucasian, Black, Native Hawaiian or Other Pacific Islander, Asian, American Indian or Alaska Native, Other)
- geographic region (US, Europe, Israel)
- ECOG performance status (0 vs 1-2)
- visceral disease (yes, no)
- histology (ductal, lobular, other)
- number of lines of prior cytotoxic chemotherapy (not including hormonal therapy) for advanced/metastatic disease, (0, 1-2)
- prior platinum treatment (no vs yes)
- germline mutation (BRCA-1 vs BRCA-2 vs both)

These subgroup analyses will be reported as forest plots containing the treatment effect hazard ratios and 95% 2-sided Wald CIs in each subgroup originating from the Cox model.

Two key subgroup analyses are defined: those by prior platinum treatment and the subgroups by BRCA mutation type. These two subgroup analyses will be supplemented with Kaplan-Meier curves by randomized treatment in each subgroup separately, as well as a stratified logrank test (97.5% 1-sided significance level) within each subgroup.

The subgroup analysis by BRCA mutation was already identified as a secondary endpoint in the protocol (Section 2.2.2). The key subgroup analysis for prior platinum treatment is added in this SAP, after the eligibility criteria related to prior platinum treatment have been weakened in amendment 4.0.

6.11.3 Secondary efficacy endpoints

6.11.3.1 Overall survival (OS) (key secondary endpoint)

This endpoint considers the following as events:

- death (Section 6.10)

This endpoint is defined as the time from randomization until the date of death (Section 6.11.1), if the patient died. If the patient did not experience an event, he/she will be censored at the last follow-up date (Section 6.2.2).

The primary analysis of this endpoint will be performed using a stratified log-rank test, performed at the 1-sided 0.025 significance level, in the OS-AR. The randomization factors will be used as the strata for this test.

Sensitivity analyses

- The analysis mentioned above will be repeated in the per protocol population, to assess the robustness of the primary result
- The analysis mentioned above will be repeated in the full ITT population, to assess the robustness of the primary result when including patients who were not centrally confirmed to be BRCA positive.
- A non-stratified log-rank test will also be performed to assess the robustness of the primary result.
- A multivariate Cox model will be fitted to assess the robustness of the treatment effect when adjusting for (potential) prognostic factors and (potential) imbalances therein. The Cox model (with Breslow ties) will be constructed based on a backward stepwise selection method, with a two-sided 0.10 cutoff for selection, and forcing treatment arm to stay in the model. The following factors will be considered for inclusion in the model:
    - Age (< 55,55-70,>70)
    - ECOG performance status (0 vs 1-2)
    - visceral disease (yes, no)
    - histology (ductal, lobular, other)
    - number of lines of prior cytotoxic chemotherapy (not including hormonal therapy) for advanced/metastatic disease (0, 1-2)
    - prior platinum treatment (no vs yes)
    - germline mutation (BRCA-1 vs BRCA-2 vs both)

Cases with missing values for 1 of the above factors are excluded from the model (when the factor is included in that model).

The reporting of this analysis will contain in 1 table:

- the fitted univariate Cox models for each of the factors (Hazard ratio for each factor and 95% 2-sided Wald CI)
- the fitted full multivariate Cox model (Hazard ratio for each factors and 95% 2-sided Wald CI)
- the multivariate Cox model after model selection as described above (hazard ratio for each factors and 95% 2-sided Wald CI, Type III test p-value for each factor)

6.11.3.2 Progression-free Survival (PFS) per investigator assessment of progression

This endpoint is defined as the time from randomization until the minimum of the date of death (Section 6.11.1) and the date of disease progression, as reported by the investigator.

For the primary analysis, per protocol, the definition for investigator reported PFS is the same as for PFS per central review, using investigator-reported PD dates instead of centrally reviewed PD dates. This is detailed below:

This endpoint considers the following as events:

- death (Section 6.10)
- disease progression as reported by the investigator (Section 6.11.1)

If the patient did not experience an event, he/she will be censored. See table 2 below for more detailed censoring and event rules for this endpoint.

A documented radiological assessment is defined as the radiologic (CT or MRI) disease assessment taking place before the start of the new anticancer treatment (Section 6.11.1), if applicable.

Table 2: Censoring rules for the endpoint of progression-free survival per investigator assessment

Condition	Date of event /censoring	Censoring	Event
No baseline tumor assessments	Date of randomization	Yes	No
No documented progression, no death	Date of last documented radiologic assessment In the event that only baseline tumor assessments are available, the date of randomization	Yes	No
Documented Progression	Date of radiological assessment showing disease progression	No	Yes
Treatment discontinuation for undocumented progression, or Toxicity or any other reason (apart from documented progression)	Date of last documented radiologic assessment	Yes	No
New anti-cancer treatment started	Date of last documented radiologic assessment before initiation of new anti-cancer treatment	Yes	No
Death before first PD assessment	Date of death	No	Yes
Death in between 2 adequate assessment visits *	Date of death	No	Yes
Death or progression after more than one missed adequate assessment visits *	Date of last documented radiologic assessment before the missed visits	Yes	No

* Adequate on-protocol imaging requires an assessment every 6 weeks (± 7 days) until Month 12 and every 9 weeks (± 7 days) thereafter, from start of protocol treatment until progression or start of subsequent anticancer treatment.

The main analysis of this endpoint will be performed using a stratified log-rank test, performed at the 1-sided 0.025 significance level. The randomization factors will be used as the strata for this test.

Sensitivity analyses

- The analysis mentioned above will be repeated in the per protocol population, to assess the robustness of the primary result.
- The analysis mentioned above will be repeated in the full ITT population, to assess the robustness of the primary result when including patients who were not centrally confirmed to be BRCA positive.
- A non-stratified log-rank test will also be performed to assess the robustness of the primary result.

6.11.3.3 Response to treatment

Response to treatment will be reported **for all patients** in the centrally confirmed ITT population by randomized treatment arm:

- Tabulation of the best overall response to treatment (complete response [CR], partial response, stable disease [SD], disease progression [PD], early death, not assessable/evaluable) by medical review (formdm01: *respev*).
- Tabulation of overall response rate (CR or partial response) by medical review (formdm01: *respev=1,2* versus *respev=3,4,5,8*); for each treatment arm, the response rate if supplemented by a 2-sided 95% CI (Pearson-Clopper method). The Pearson's chi-square test for association will be performed to compare the overall response rate (ORR) between treatment arms and the corresponding p-value will be displayed.

Duration of response to treatment will be reported in the efficacy population, restricted to those patients who obtained a response (CR or partial response) by medical review (formdm01: *respev=1,2*), by randomized treatment arm.

- The duration of response is calculated as the time from response until the first event of investigator-reported disease progression or death whichever occurs earlier (Section 6.11.3.2). The same censoring rules as for investigator-reported disease progression apply (Section 6.11.3.2). The duration of response will be reported using the Kaplan-Meier method. Kaplan-Meier curves by randomized treatment arm will be shown. Medians - if reached - will be presented with a 2-sided 95% CI, based on the nonparametric method (Brookmeyer & Crowley, 1982).

6.11.3.4 Time to treatment failure

Time to treatment failure considers the following as events:

- End of protocol treatment for any reason (including death) (formeot: *dtlast*)
- Disease progression as reported by the investigator (Section 6.11.1)

Time to treatment failure is defined as the time from randomization until the date of the first event (date of last treatment administration on end of treatment form). If the patient does not experience an event, he/she will be censored at the last dose date or last tumor assessment date whichever occurs later (Section 6.2.2).

Patients that never started any protocol treatment will be censored at time of randomization.

The main analysis of this endpoint will be performed using a stratified log-rank test, performed at the 1-sided 0.025 significance level. The randomization factors will be used as the strata for this test.

Sensitivity analyses

- The analysis mentioned above will be repeated in the per-protocol population, to assess the robustness of the primary result
- The analysis mentioned above will be repeated in the full ITT population, to assess the robustness of the primary result when including patients who were not centrally confirmed to be BRCA-positive.
- A non-stratified log-rank test will also be performed to assess the robustness of the primary result.

6.12 Interim analysis for futility for progression free survival

This interim analysis will be reported in the centrally confirmed ITT population.

PFS by central independent review will be analyzed as specified in Section 6.11.2.

A CCD for the interim analysis will be determined based on an estimate of when the required 93 events will be reached. At time of database lock, the true number of observed events can be slightly more or less than 93. A gamma family beta-spending function with a non-binding gamma (γ=-5) stopping boundary based on the actual number of PFS events at the time of interim analysis data cutoff and the minimum total target number of events of 137 will be used for the interim futility analysis of PFS (i.e. the information fraction for futility analysis is equal to the number of events observed at the interim analysis divided by 137). The futility boundary will be assessed by the EAST 6 software).

Based on the accrual rate and PFS median assumptions, the enrollment will be done after 137th event and the final PFS analysis will be done at the end of enrollment. The information fraction calculated based on 137 events will be larger than the information fraction calculated based on the total number of events at the end of enrollment. This larger information fraction will yield a smaller hazard ratio futility boundary which allows the trial to be stopped more easily if the experiment drug is not efficacious.

In order to fully evaluate the interim data, the projected numbers of PFS and OS events by the end of enrollment will be provided in the IDMC reports. The projections will be done using the interim data based on the following:

1. Past accrual and projected future accrual
2. Observed PFS rates and assumptions going forward
3. Observed death rates and assumptions going forward.

6.13 Interim analysis for overall survival

An interim analysis for overall survival will be reported in the centrally confirmed ITT population at the time of the final PFS analysis.

This interim analysis will be performed using the locked database for the FAR. OS will be analyzed as specified in Section 6.11.3.1.

The interim analysis rule for early efficacy will be assessed using the EAST 6 software, using the original design (i.e. target number of events) as implemented in the protocol (version 6, January 13, 2017). The interim analysis will utilize O'Brien-Fleming type boundaries derived from the Lan DeMets alpha spending function based on the actual number of events observed at the time of the interim analysis.

6.14 Quality of Life

Before the database lock for the FAR, the database will be checked for compliance to the HRQoL schedule detailed in Section 10.4.1 of the protocol (version 6, January 13, 2017). The following considerations are subject to the outcome of this compliance review and will be detailed in a separate SAP which will be finalized before the database lock.

Statistical considerations

Data from the EORTC quality of life questionaire-C30 (QLQ-C30) will be scored according to the algorithm described in the EORTC scoring manual. All scales and single items are scored on categorical scales, and are linearly converted to 0-100 scales.

The primary health-related quality of life (HRQoL) endpoint considered relevant for this study is time to HRQoL deterioration (TTQ). TTQ is defined as the time from randomization to the first observed of the following events:

- death (Section 6.10)
- disease progression (Section 6.11.1)
- deterioration in any of the following QLQ-C30 scales: fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, physical functioning, role functioning, social functioning and emotional functioning or global health/quality-of-life (QoL) scale. Patients are

considered to have deteriorated for a given scale if a worsening of 10 points at any time point after baseline is observed. A change of 10 points or more is considered to be clinically relevant.

Patients who have not experienced an event at the time of analysis will be censored at the time of the last completed HRQoL assessment. All patients who have a baseline and at least one follow- up HRQoL assessment will be included in the TTQ analysis.

TTQ will be calculated using Kaplan–Meier method and compared using the two-sided log-rank test across the randomized arms. TTQ will be described using medians and hazard ratio with 95% CIs.

To assess the robustness of the results, the following sensitivity variants to the TTQ endpoint will be investigated:

- TTQ1 – time from randomization to death, treatment discontinuation, or deterioration in any of the selected QLQ-C30 scores (treatment discontinuation instead of progression)
- TTQ2 – time from randomization to death or deterioration in any of the selected QLQ-C30 scores (excluding progression as event)
- TTQ3 – time from randomization to deterioration in any of the selected QLQ-C30 scores (excluding both death and progression)
- TTQ4 – time from randomization to death, disease progression, or deterioration in any of the following QLQ-C30 scores: fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea (limit only to symptom deterioration).

These alternative formulations serve only to investigate the robustness of the main results. They do not replace the primary endpoint. In the event that a significant difference is found in TTQ, the endpoint will be split up by its various events (death, disease progression, and the selected scales) to investigate the treatment effect on each of these components.

In addition, the following summary statistics per-patient will be calculated for the secondary objectives as sensitivity analyses and to complement the interpretation of the time-to-event model:

- average change from baseline during the on-protocol treatment period
- average change from baseline during the off-protocol treatment period
- 10-point worsening from baseline during the on-protocol treatment period (y/n)
- 10-point worsening from baseline during the off-protocol treatment period (y/n)

These statistics will be compared between the 2 groups using non-parametric Wilcoxon rank test (for the summary statistics based on average change) or Fisher exact test (for the summary statistics based on 10-point worsening). Results will be summarized by the appropriate statistical estimation and corresponding 95% CI. For the 2 binary summary statistics, missing data due to attrition will be imputed as worsening for sensitivity purposes.

All available scales from the QLQ-C30 will be summarized per treatment arm on an exploratory basis.

Missing data

Missing data is a potential major source of bias in HRQoL assessment.

To check the potential impact of missing HRQoL data in the study, the compliance mechanism will be investigated prior to initiating the HRQoL analysis. HRQoL compliance at a certain assessment time (T_i) will be defined as the ratio of the number of valid forms received over the number of forms expected at that time:

$$Compliance(T_i) = \frac{valid\ QoL\ forms\ within\ [L_i\ ,\ U_i]}{QoL\ expected\ \ at\ T_i}$$

where L_i and U_i are the lower and upper bound of the time windows associated with T_i. HRQoL forms will be considered as invalid if no validated completion date was provided, the completion date falls outside of the time windows, multiple HRQoL forms were received during the time window (the form closest to the assessment date will be kept), a wrong version or wrong translation of questionnaire was used, or the form was filled out by an unauthorized person. QoL forms are expected at T_i for each patient who was within the QoL assessment schedule, ie, alive at time T_i. Reasons for non-completion if an assessment was missed will be collected via the CRFs. Characteristics of patients with and without valid HRQoL data will be compared,

and trends over time per dropout pattern will be investigated. Model building will be used to investigate whether the compliance mechanism is linked to selected prognostic variables.

Once the main analysis is completed, sensitivity analyses will be undertaken to verify the robustness of the results vis-à-vis the missing data.

In the event that overall compliance is deemed too low (< 50%), only an exploratory analysis will be performed in lieu of the main analysis.

7 Overview table for the 4 analysis reports

Section	Section title	IDMC-PFS	FAR	IDMC-OS*	OS-AR
6.2	Patient availability	X	X		X (only sections 6.2.2 and 6.2.4)
6.5	Baseline characteristics	X	X		
6.6	Compliance to the protocol	X	X		
6.7	Exposure to treatment	X	X		X (limited to relative dose intensity and number of cycles received)
6.8	Safety evaluations	X	X		X
6.9	Reasons for stopping treatment	X	X		X
6.10	Disease status	X	X (excluding deaths not pertaining to the primary endpoint)	X (limited to deaths)	X
6.11.2	Primary endpoint: PFS by independent central review		X		X
6.11.3.1	Overall survival	X (excluding sensitivity analyses)			X
6.11.3.2	PFS per investigator assessment		X		X
6.11.3.3	Response to treatment		X		X
6.11.3.4	Time to treatment failure		X		X
6.12	Interim analysis for futility for PFS	X			
6.13	Interim analysis for overall survival			X	

6.14	Quality of Life		X		X

* In addition, the IDMC is supplied with the FAR

8 Bibliography

Brookmeyer, R., & Crowley, J. (1982). A confidence interval for the median survival time. *Biometrics*, 29-41.

Lin, D., Wei, L., & Ying, Z. (1993). D.Y. Lin, L.J. Wei et al (1993). Checking the Cox model with cumulative sums of martingale-based residuals. *Biometrika*, 557-572.

Schemper, M., & Smith, T. (1996). A note on quantifying follow-up in studies of failure time. *Controlled clinical trials*, 343-346.

9 Appendix 1: List of case report forms (CRFs)

SAS Form code	Form name
form905	health economics questionnaire
form930	QoL C-30
formae	adverse events form
formcenbrca	central BCRA mutation test form
formdm01	medical review form
formdh	disease history form
formmh	medical history form
formeot	end of treatment form
formfu	follow-up form
formfum	follow-up measurements form (RECIST 1.1)
formim	initial measurements form (RECIST 1.1)
formlbbio	biochemistry form
formlbhem	hematology form
formmyh	myelosuppresion history form
formnllab	normal ranges lab form
formothbrca	previous brca mutation test form
formpe	physical examination form
formsf	screening failure form
formtrtc	capecitabine treatment form
formtrte	eribulin treatment form
formtrtg	gemcitabine treatment form
formtrtn	niraparib treatment form
formtrtviv	IV vinorelbine treatment form
formtrtvo	oral vinorelbine treatment form
formrg1	screening-registration form (values provided at time of screening)
formrg2	eligibility checklist form (values provided at time of randomization)
formcrg1	screening-registration form (potentially corrected values)
formcrg2	eligibility checklist form (potentially corrected values)
patient	patient identifier form

10 Appendix 2: Tables and listing to be provided to IDMC for safety review

Output Type (T/L/F)	Number	Title	Analysis Set
Accrual information			
T	I.1	Cumulative Proportion of Subjects Randomized by Calendar Time	Full ITT population
F	F.1	Subject Accrual over time	Screening population
T	I.2	Subject Accrual by site	Screening population
T	I.3	Number of patients registered per site	Screening population
F	F.2	Number of patients registered per site	Screening population
T	I.4	Accrual by country	Screening population
Study Conduct and Patient Disposition			
T	C1	Eligibility status	Full ITT population
L	C.2	Listing of ineligible patients	Full ITT population
T	C.3	Compliance to treatment allocation	Full ITT population
T	C.4	Patient disposition and reason for discontinuation	Full ITT population
L	C.5	Listing of patients who are not treated as randomized	Full ITT population
Kaplan-Meier	C.6	Time to protocol treatment discontinuation	Full ITT population
T	C.7	Distribution of stratification factors	Full ITT population
L	C.8	Listing of patients who are lost-to-follow-up/withdrew from study	Full ITT population
Baseline data			
T	B.1	Demographic characteristics	Full ITT population
T	B.2	Primary Diagnoses and time since diagnosis	Full ITT population
T	B.3	Baseline Characteristics (incl. ECOG Performance Status)	Full ITT population
Study Treatment Exposure			
T	T.1	Number of cycles received	Safety population
T	T.2	Dose Interruptions, Reductions - overall	Safety population
T	T.3	Dose Interruptions, Reductions – by cycle	Safety population
T	T.4	Reason for first dose interruption/reduction	Safety population
T	T.5	Reason for stopping protocol treatment	Safety population
Adverse Events Data			
T	A.1	Discontinuations Due to toxicity	Safety population
T	A.2	Temporary Discontinuations or Dose Reductions Due to toxicity	Safety population

T	A.3	Overall Summary of Adverse Events (worst grade during treatment)	Safety population
Kaplan-Meier	F.3	Kaplan-Meier Plots of Time to First Occurrence of Most Common Treatment Related grade 3-4 Adverse Events	Safety population
T	A.4	Cause of Death	Safety population
L	A.5	Listing of Deaths and the cause	Safety population
L	A.6	Listing of serious Adverse Events	Safety database
L	A.7	Listing of (likely) treatment related adverse events that led to drug discontinuation	Safety population
L	A.8	Listing of grade ≥ 3 Adverse events	Safety population
Laboratory Data			
T	L.1	Laboratory Results Summary by Maximum CTC Grade (Hematology, Cycle 1)	Safety population
T	L.2	Laboratory Results Summary by Maximum CTC Grade (Hematology, By Cycle, All cycles)	Safety population
T	L.3	Laboratory Results Summary by Maximum CTC Grade (Chemistries, All Cycles)	Safety population
T	L.4	Laboratory Results Summary by Maximum CTC Grade (Chemistries, Cycle 1)	Safety population
L	L.5	Listing of CTC grade ≥ 3 (chemistries/hematology)	Safety population