Statistical Analysis Plan

Official Title of Study: AN OPEN-LABEL, SINGLE-ARM PILOT STUDY EVALUATING THE ANTITUMOR ACTIVITY AND SAFETY OF NIRAPARIB AS NEOADJUVANT TREATMENT IN LOCALIZED, HER2-NEGATIVE, BRCA-MUTANT BREAST CANCER PATIENTS

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STATISTICAL ANALYSIS PLAN: Study 3000-01-005

Study Title: An Open-Label, Single-Arm Pilot Study Evaluating the Antitumor Activity and Safety of Niraparib as Neoadjuvant Treatment in Localized, HER2-Negative, BRCA-Mutant Breast Cancer Patients

Study Number: 3000-01-005

Study Phase: 2

Product Name: Niraparib

Sponsor: TESARO, Inc.

Sponsor Contact: 1000 Winter Street
Waltham MA 02451

	Version	Version Date
Original Statistical Analysis Plan:	V0.6	02/11/2019

Niraparib
Protocol No. 3000-01-005 Statistical Analysis Plan TESARO, Inc. 02/11/2019

SPONSOR SIGNATURES

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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.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
ALK	anaplastic lymphoma kinase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BRCA	breast cancer susceptibility gene
BRCAmut	breast cancer susceptibility gene mutant
BMI	body mass index
BOR	best overall response
CI	confidence interval
CBC	complete blood count
CR	complete response
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Easter Cooperative Oncology Group
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
EOS	end of study
EOT	end of treatment
FDA	US Food and Drug Administration
ER-	Estrogen receptor negative
ER+	Estrogen receptor positive
HER2-	human epidermal growth factor receptor 2 negative
HRD	homologous recombination deficiency
LLN	lower limit of normal
LOH	loss of heterozygosity
MedDRA	Medical Dictionary for Regulatory Activities
PARP	poly(ADP-ribose) polymerase
pCR	pathological complete response

Abbreviation	Definition
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetics
PO	oral(ly)
PR	partial response
PR-	progesterone receptor negative
PR+	progesterone receptor positive
Q1	first quartile
Q3	third quartile
QD	once daily
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
SD	stable disease or standard deviation
TEAE	treatment-emergent adverse event
TNBC	triple-negative breast cancer
ULN	upper limit of normal
WHO	World Health Organization

1 INTRODUCTION

This statistical analysis plan (SAP) provides the detailed statistical methods to be used for analyses and data presentation for reporting efficacy and safety of investigational drug niraparib for TESARO study protocol 3000-01-005.

The pharmacokinetics and exposure-response analyses will be provided in a separate document. The exploration of blood and tumor-based biomarkers that predict sensitivity or resistance to niraparib will also be detailed in a separate document.

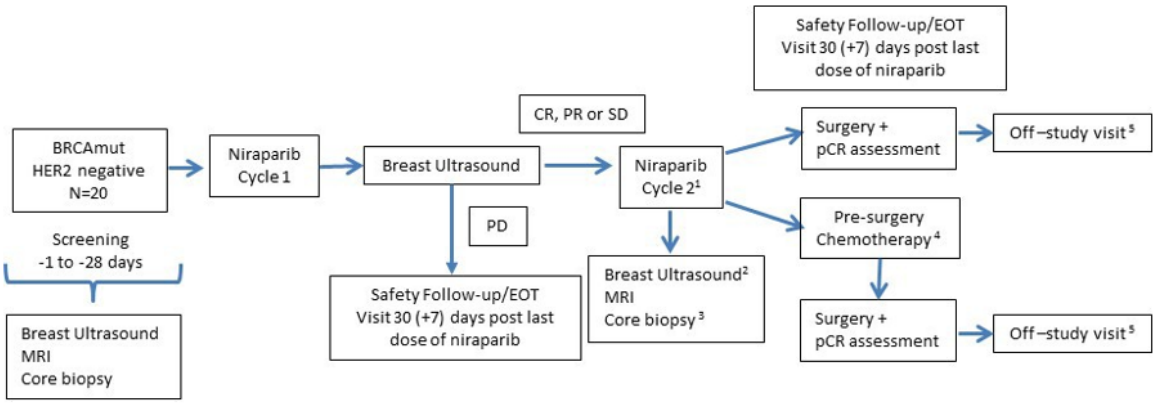
This document has been prepared according to Study Protocol Version 2 dated 01 August 2018.

2 STUDY DESIGN OVERVIEW

2.1 Overall Study Design

This is an open-label, single-arm pilot study evaluating the antitumor activity and safety of niraparib as neoadjuvant therapy in patients with human epidermal growth factor receptor 2 (HER2) negative and breast cancer susceptibility gene mutant (*BRCA*mut) localized breast cancer (primary tumor ≥1 cm). The study design is summarized in the schema below. If antitumor activity in the *BRCA*mut cohort is demonstrated, the protocol may be amended to add a homologous recombination deficiency (HRD)-positive, *BRCA*-wild type cohort. The study design is presented graphically as below.

Study Schema:



[1]Patients may receive up to 6 months of niraparib.
[2]Breast ultrasounds are performed at the end of each month for those patients receiving additional cycles.
[3]Core biopsy will be obtained preferably within 24 hours of the last dose of niraparib in cycle 2 and prior to any subsequent anticancer therapy or procedure. A surgical biopsy may be used in lieu of a core biopsy provided that surgery occurs within 24 hours of the last dose of niraparib in Cycle 2.
[4]Tumor size cut-off for pre-surgery chemotherapy will be determined by investigator discretion.
[5]Off-study visit is for the collection of pCR results for patients for whom the Safety Follow-up/EOT Visit occurred prior to surgery; for all other patients the Safety Follow-up/EOT Visit will act as the off-study visit.

This study will consist of a Screening Period (Day -28 to Day -1), a Treatment Period, Presurgery chemotherapy (if appropriate), Surgery, a Safety Follow-up/EOT visit occurring 30 days (+ 7 days) after the last dose of study medication, and an Off-Study Visit for the purposes of collecting the pathological complete response (pCR) results for patients for whom the Safety Follow-up/EOT Visit occurred prior to surgery; for all other patients the Safety Follow-up/EOT Visit will act as the off-study visit.

The schedules of assessments are presented in Table 1.

Table 1: Schedule of Events

Cycle/Visit:	**Screening**	**Cycle 1 ± 7 days**					**Cycle 2 ± 7 days**		**Cycles 3-6 ± 7 days (if applicable)**		**Pre-surgery**	**Surgery**	**Safety Follow-Up/EOT Visit**
Day of Procedure	**-28 to -1**	**1**	**8**	**15**	**21**	**28**	**1**	**28**	**1**	**28**			**30 + 7 days post last dose of niraparib**
Informed consent	X												
Inclusion/exclusion criteria review	X												
Demographics	X												
Medical, surgical, cancer, and medication history	X												
Local Confirmation HER2 negative and ER, PR status	X												
Blood sample for exploratory biomarkers (ctDNA)	X					X[2]		X[2]			X[3]		
BRCA1/2 mutation testing[1]	X												
Completion of neo-adjuvant chemotherapy eCRFs, if applicable											X		

Table 1: Schedule of Events

Cycle/Visit:	**Screening**	**Cycle 1 ± 7 days**					**Cycle 2 ± 7 days**		**Cycles 3-6 ± 7 days (if applicable)**		**Pre-surgery**	**Surgery**	**Safety Follow-Up/EOT Visit**
Day of Procedure	**-28 to -1**	**1**	**8**	**15**	**21**	**28**	**1**	**28**	**1**	**28**			**30 + 7 days post last dose of niraparib**
Breast ultrasound tumor assessment	X					X[4]		X[4]		X[4]			
Breast MRI tumor assessment	X							X[4]					
Core biopsy	X							X[5]				X[5]	
pCR assessment												X	
Laboratory assessments:													
CBC	X	X[6]	X	X	X		X[6]		X[6]				X
Serum chemistry	X	X[6]		X			X[6]		X[6]				X
Pregnancy test	X[7]	X[7]											X
Urinalysis	X												
ECG	X												

Table 1: Schedule of Events

Cycle/Visit:	**Screening**	**Cycle 1 ± 7 days**					**Cycle 2 ± 7 days**		**Cycles 3-6 ± 7 days (if applicable)**		**Pre-surgery**	**Surgery**	**Safety Follow-Up/EOT Visit**
Day of Procedure	**-28 to -1**	**1**	**8**	**15**	**21**	**28**	**1**	**28**	**1**	**28**			**30 + 7 days post last dose of niraparib**
Complete physical examination	X												X
Symptom-directed physical examination		X					X		X				
Physical breast examination	X	X					X						X
Vital signs and weight	X	X					X		X				X
Height	X												
ECOG performance status	X												X
Concomitant medications and procedures	X	Recorded from informed consent through Safety Follow-up/EOT											
Adverse event monitoring[8]	X	Recorded from informed consent through 30 days post-treatment											
Niraparib study drug dispensed/collected		X					X		X				

Table 1: Schedule of Events

Cycle/Visit:	**Screening**	**Cycle 1 ± 7 days**					**Cycle 2 ± 7 days**		**Cycles 3-6 ± 7 days (if applicable)**		**Pre-surgery**	**Surgery**	**Safety Follow-Up/EOT Visit**
Day of Procedure	**-28 to -1**	**1**	**8**	**15**	**21**	**28**	**1**	**28**	**1**	**28**			**30 + 7 days post last dose of niraparib**
PK Sample Collection		X[9]					X[9]						

Abbreviations: AESI = adverse events of special interest; AML = acute myeloid leukemia; *BRCA* = breast cancer susceptibility gene; CBC = complete blood count; ctDNA = circulating tumor deoxyribonucleic acid; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EOT = end of treatment; ER = estrogen receptor; IEC = Independent Ethics Committee; IRB = Institutional Review Board; MDS = myelodysplastic syndrome; pCR = pathological complete response; PK = pharmacokinetic; PR = progesterone receptor; SAE = serious adverse event.

[1] If *BRCA* status is known, it need not be repeated. Results may have been obtained by either local or central laboratory testing.

[2] Can be collected pre-dose Day 1 of the next cycle.

[3] Pre-surgery blood sample is not required for patients proceeding directly to surgery at the end of Cycle 2.

[4] Can be performed +/- 3 days from Day 28, but results must be available prior to the start of the next cycle.

[5] Core biopsy should be obtained on Cycle 2 Day 28 (+7 days) within 24 hours of last dose of niraparib and prior to ultrasound, MRI, and any subsequent anticancer therapy or procedure. A surgical biopsy may be used in lieu of a core biopsy provided that surgery occurs within 24 hours of the last dose of niraparib in Cycle 2.

[6] Cycle 1 Day 1 testing not required if screening assessments were performed within 72 hours of Day 1.

[7] A serum pregnancy test will be performed locally for all women of childbearing potential at Screening (within 72 hours prior to the first dose of study drug). The result must be negative before the first dose of study drug is administered. If the serum pregnancy result is not available before dosing, a urine pregnancy test may be performed. Pregnancy tests may also be repeated during the study if requested by an IEC/IRB or if required by local regulations.

[8] SAEs and AESIs concerning hypertension and hematologic toxicities will be collected and recorded in the eCRF and on an SAE report form for each patient from the date of signed informed consent until 90 days after the last dose of study drug (or until the start of alternate anticancer therapy, whichever occurs first). AESIs concerning MDS/AML, secondary cancers, pneumonitis, and embryo-fetal toxicity must be collected and reported to the Sponsor for each patient from the date of signed informed consent until study closeout.

[9] Samples for PK assessment with be collected on Day 1 of Cycles 1 and 2 predose, 2 (± 30 minutes) and 4 (± 30 minutes) hours post dose, and in conjunction with the post-treatment core biopsy.

2.2 Sample Size

No formal sample size calculation has been done for this study. The sample size is determined based on the clinical considerations only.

A total of approximately 20 evaluable patients will be enrolled. This sample size should be sufficient for signal finding prior to initiating a larger study. For example, it will provide approximately 80% power with 1-sided significance level of 0.15 to differentiate a response rate of 80% from a minimum response rate of 60%. Other examples are provided below in Table 2.

Table 2: Powers with Different Response Rates

One-sided alpha	Minimum Response Rate	Niraparib Response Rate	Power
0.15	60%	70%	45%
0.15	60%	75%	65%
0.15	60%	80%	80%

2.3 Randomization and Blinding

This is an open-label study and patients will not be randomized.

3 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective of this study is:

- To evaluate the preliminary antitumor activity of niraparib assessed as the tumor response rate based on the change in tumor volume as measured by breast MRI, observed after treatment with niraparib in the neoadjuvant treatment of localized, HER2 negative, breast cancer susceptibility gene mutant (*BRCA*mut) breast cancer patients.

3.2 Second Objectives

The secondary objectives of the study are as follows:

- To evaluate the preliminary antitumor activity of niraparib assessed by:
  - Presence of pCR defined as ypT0/Tis ypN0 by receipt of pre-operative chemotherapy (Yes versus No)
  - Percentage change in tumor volume from baseline after 2 months of niraparib treatment by MRI and ultrasound
  - Tumor response rate based on the change in tumor volume as measured by breast ultrasound
- To evaluate safety and tolerability of niraparib per National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.03 criteria

3.3 Exploratory Objectives

- To evaluate niraparib-induced changes in immune responses
- To explore intra-tumoral niraparib concentration and correlation with blood
- To estimate the preliminary antitumor activity of niraparib in BRCAmut triple-negative breast cancer (TNBC) patients and BRCAmut hormone-positive (HR+) patients
- To evaluate pharmacodynamic inhibition of poly(ADP-ribose) polymerase (PARP) activity in the tumor
- To explore molecular biomarkers related to disease biology or response to treatment using tumor tissue or liquid biopsy approaches (e.g. ctDNA)

4 STUDY ENDPOINTS AND EVALUATIONS

4.1 Efficacy Endpoints

4.1.1 Primary Efficacy Endpoint

Tumor response rate based on the change in tumor volume as measured by breast MRI; a response is considered at least >30% reduction of tumor volume from baseline after 2 months of niraparib treatment without any new lesion development. Tumor volume will be calculated as (length × width × height × π)/6. The percentage reduction in tumor volume will be set as 99% if the tumor becomes too small to measure at the post-baseline visit.

4.1.2 Secondary Efficacy Endpoints

- pCR is defined as ypT0/Tis ypN0 by receipt of pre-operative chemotherapy (Yes vs. No). pCR is defined as the absence of residual invasive cancer on hematoxylin and eosin evaluation of the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy (i.e., ypT0/Tis ypN0 in the current AJCC staging system [Appendix D]).
- Tumor response rate based on the change in tumor volume as measured by breast ultrasound; a response is considered at least >30% reduction of tumor volume from baseline after 2 months of niraparib treatment without any new lesion development. Tumor volume will be calculated as (length × width × height × π)/6.
- Percentage change in tumor volume from baseline after 2 months of niraparib treatment as measured by ultrasound. Tumor volume will be calculated as (length × width × height × π)/6. The percentage reduction in tumor volume will be set as 99% if the tumor becomes too small to measure at the post-baseline visit.
- Percentage change in tumor volume from baseline after 2 months of niraparib treatment as measured by MRI. Tumor volume will be calculated as (length × width × height × π)/6. The percentage reduction in tumor volume will be set as 99% if the tumor becomes too small to measure at the post-baseline visit.

4.1.3 Exploratory Efficacy Endpoints

- Immune-related changes in gene expression profiles and cellular composition (eg, T-cells, myeloid cells, and natural killer cells) in pre vs. post niraparib treatment tumor samples
- Niraparib concentration in post treatment tumor samples and correlation with PK in peripheral blood
- Estimation of change in tumor volume in BRCAmut TNBC patients and in BRCAmut hormone-positive patients

- Comparison of PARP enzymatic activity (eg, PARylation), DNA damage and repair (eg, phosphorylated histone H2AX, RAD51), proliferation (eg, Ki67) and survival (eg, Caspase 3) in pre vs. post niraparib treatment tumor samples
- Potential biomarkers of sensitivity or resistance (e.g. BRCA reversion mutations, loss of heterozygosity [LOH]) in ctDNA or tumor tissue
- Targeted (or whole exome) sequencing for other disease related molecular alterations with remaining blood or tumor samples

Except for the third bullet point, analysis plan for other exploratory endpoints will be provided separately.

4.2 Safety Evaluations

The safety evaluations include:

- Treatment emergent adverse events (TEAEs)
- Extent of exposure
- Clinical laboratory assessments
  - Hematology
  - Chemistry
- Serum or urine pregnancy testing
- Vital signs
- Physical examination findings
- Physical breast examination
- ECG

4.3 Other Evaluations

Other evaluations include:

- Demographics and baseline characteristics (including BRCA mutation test and hormone receptor test)
- Medical history
  - Disease history (breast cancer history)
  - Other cancer history
  - Medical history
  - Surgical history
  - Prior blood disorders
- Medication use/procedures
  - Prior and concomitant medication/therapy
  - Prior anticancer treatment for non-primary cancer
  - Growth factors

  - Transfusions
  - Concomitant procedures/surgeries
  - Prior and concomitant radiotherapy
  - Concomitant chemotherapy
  - Neoadjuvant chemotherapy (post niraparib)
- ECOG Performance status
- Urinalysis
- Drug accountability (Niraparib)
- Surgery and tumor sample collection
- MRI primary and non-primary lesion assessments
- Ultrasound primary and non-primary lesion assessments
- New lesion assessment
- Niraparib dose modification
- Evaluation of response on primary lesion based on MRI and ultrasound

5 PLANNED ANALYSES

5.1 Changes from planned Analyses in the Protocol

There are no changes from planned Analyses in the Protocol.

5.2 Interim Analyses

There are no planned interim analyses.

5.3 Final Analyses and Reporting

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

6 ANALYSIS POPULATIONS AND APPLICATIONS

Statistical analysis and data tabulation will be performed using the following analysis populations unless specified otherwise:

6.1 Efficacy Evaluable Population

Efficacy Evaluable (EE) population includes all patients who complete 2 cycles of treatment. The EE population will be the primary analysis population for the efficacy analyses. The patients need to have an observed outcome at the end of cycle 2 in order to be included in the analysis based on the EE population.

6.2 Full Analysis Population

Full Analysis Set (FAS) includes all patients who receive at least one dose of study medication and have at least one ultrasound scan at Month 1.

6.3 Pharmacokinetic Population

Pharmacokinetic (PK) population includes all patients who receive at least one dose of study medication and have at least one post-dose niraparib concentration.

6.4 Safety Population

Safety population includes patients who receive at least one dose of study medication. The safety population will be the primary analysis population for the safety analyses.

6.5 Application of Analysis Populations

The analysis population(s) that will be used for creating the summary table(s) of each type is provided in Table 3. All data will be presented in listings for the enrolled patients. A patient will be considered enrolled when the patient has been consented in the electronic case report form (eCRF).

Table 3: Application of Analysis Populations for Tables and Graphs

Type	Safety	EE	FAS	PK*
Disposition	X			
Demographics and baseline characteristics	X	X	X	
Protocol deviations	X			
Medical and disease history	X			
Prior and concomitant medications	X			
Summary/analyses on efficacy endpoints		X	X	
Safety evaluations	X			
Extent of Exposure	X			

* The PK analyses will be provided in a separate document.

7 STATISTICAL CONSIDERATIONS

All analyses described in this plan are considered a priori analyses in that they have been defined prior to locking the database. All other analyses, if any, designed subsequently to locking the database, will be considered post hoc analyses and will be described as exploratory analyses in the Clinical Study Report.

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

7.1 General Statistical Procedures

The descriptive statistics for continuous variables will be the mean, median, standard deviation (SD), quartiles (Q1, Q3), minimum, maximum, and number of patients.

Frequency distributions for all categorical variables will be presented using counts and percentages.

7.2 Patient Enrolment and Disposition

7.2.1 Patient Enrollment

Number of patients will be provided for each analysis population. For the Safety population, the denominators for percentages are based on number of screened patients. Screened population includes all patients who have been consented.

For other populations, the denominators for percentages are based on number of patients in the Safety population.

Enrollment information will be provided in a data listing.

7.2.2 Patient Disposition

Patient disposition will be summarized for the Safety population. The summary will present frequency distribution for patients completing the study and discontinuing from the study overall and by reason for discontinuation.

Additionally, the frequency distribution will be provided for patients discontinuing treatment niraparib by reason for discontinuation.

The denominators for calculating the percentages will be based on number of patients in the Safety population.

Discontinued patients will be provided in a data listing.

7.2.3 Protocol Deviations

A protocol deviation (PD) is any failure to comply with the study protocol as approved by the relevant regulatory authority, ethics committee and/or institutional review board, whether planned or unplanned.

PD will be assessed and classified as important or significant. A protocol deviation is classified as an important PD if there is the potential to:

- Impact the completeness, accuracy, and/or reliability of the study data, or

- Affect a subject's rights, safety, or well-being.

Important protocol deviations require review to confirm whether or not they are significant. The following are PDs that will always be considered important according to TESARO SOP 1000-00021-CLN:

- Failure to obtain informed consent for participation in the clinical trial
- Enrollment of ineligible subject
- Subject developed withdrawal criteria during the study but was not withdrawn
- Subject received incorrect treatment
- Incorrect or non-compliant dosing of a subject, i.e. dosing that is inconsistent with the protocol
- Administration of an excluded concomitant treatment to a trial subject
- Incorrect cohort assignment

A protocol deviation is classified as a significant PD if it has been confirmed to:

- Adversely impact the completeness, accuracy, and/or reliability of the study data
- Affect a subject's rights, safety, or well-being.

The TESARO medical monitor in conjunction with other study team members as appropriate may determine any PD not listed above to be important or significant based on his/her assessment of (potential) impact. Additionally, a PD could be "downgraded." In this case, the rationale for the change should be documented by the TESARO medical monitor.

Criteria for important and/or significant PDs may be updated as needed throughout the course of the clinical trial.

All PDs will be identified and finalized prior to database lock.

Number and percentage of patients with important or significant protocol deviations will be summarized by type of deviation. The denominators for calculating the percentages will be based on number of patients in the Safety population.

All protocol deviations will be listed.

7.3 Demographic and Other Pre-treatment Variables

7.3.1 Demographics/Baseline Characteristics

Patient demographics and baseline characteristics include:

- Age (years) calculated as date of screening minus date of birth / 365.25 if date of birth is reported, or age as reported on the eCRF will be used

- Age categories (18 to <65, >=65)
- Race (American Indian/Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, and Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, and Unknown)
- Baseline weight (in kilograms; if weight is reported in pounds, convert to kilograms by dividing by 2.2)
- Baseline height (in centimeters; if height is reported in inches, convert to centimeters by multiplying by 2.54)
- Baseline body mass index (BMI) (kg/m2), calculated using the patient's height and weight [BMI (kg/m2) = weight (kg) / height (m)2]
- ECOG performance status at baseline
- If female, childbearing status (Childbearing potential, Non-childbearing potential)

Continuous data will be summarized for each analysis population, using descriptive statistics.

Categorical data will be summarized with frequency distributions using counts and percentages of patients in each category. The denominators for calculating the percentages will be based on the number of patients for the Safety population.

Demographics and baseline characteristics will be provided in a listing.

7.3.2 Medical History

7.3.2.1 Breast Cancer History and Biomarkers

Breast cancer history will be collected for date of initial diagnosis, laterality, cancer stage at time of initial diagnosis, breast cancer pathology, date of biopsy, histology type, and histology grade.

Times from diagnosis to the date of first dose, laterality, stages of cancer, histopathologic type and histology grade will be summarized using descriptive statistics for continuous variables and frequency distribution for categorical variables.

Additionally, BRCA mutation test data and hormone receptor test data will be summarized as well.

Data listings will be provided for breast cancer history, BRCA mutation status and hormone receptor test results

7.3.2.2 General Medical History

The medical history will be coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA). The frequency count and percentage of patients

experiencing any medical conditions will be tabulated by MedDRA SOC and PT for each analysis population. The denominators for calculating the percentages will be based on number of patients in the Safety population.

A data listing of medical history will be provided.

7.3.2.3 Other Cancer History, Surgery History, and Prior Blood Disorders

Other cancer history will be summarized using type of cancer collected on the CRF. Similarly, prior blood disorders will be summarized using events collected on the CRF as well.

Data listings will be provided separately for prior blood disorders, other cancer history, and surgical history.

7.3.3 Medication Use/Procedures

All medications/therapies will be coded using the current version of World Health Organization (WHO) Drug Dictionary. The count and percentage of patients who took prior/concomitant medications and anticancer treatment will be provided separately for each analysis population using therapeutic class and WHO Drug preferred name. The denominators for calculating percentages will be based on the number of patients in each Analysis population. For the summary tables, if a patient has taken a prior or concomitant medication/subsequent treatment more than once, the patient will be counted only once for the medication/treatment.

Prior medications are defined as medications received prior to the first dose of either study drugs. Concomitant medications are defined as medications that were received after the first dose of study medication.

In addition, prior anticancer treatment for non-primary cancer will be summarized for any prior anticancer treatments received, reason for administration, numbers of prior anticancer treatments (treated as both continuous variable and categorical variable [i.e., 0, 1, 2, 3, 4, or >=5]), and time since the end of last prior anticancer treatment (months).

All medications and prior anticancer treatment for non-primary cancer will be provided in data listings. In addition, separate listings will be provided for:

- Growth factors
- Transfusions
- Concomitant Procedures/surgeries
- Prior and concomitant radiotherapy
- Concomitant chemotherapy
- Neoadjuvant chemotherapy (post niraparib)

7.4 Analysis of Efficacy Data

No formal statistical testing will be done for efficacy endpoints.

7.4.1 Primary Efficacy Data

Tumor response measured by breast MRI is defined as at least >30% reduction of tumor volume from baseline after 2 months of niraparib treatment without any new lesion development.

Number of tumor responders measured by breast MRI, tumor response rate and its 95% binomial exact (Clopper-Pearson) confidence interval will be reported.

7.4.2 Secondary Efficacy Data

pCR and tumor responder measured by breast ultrasound will be analyzed using the same methods for tumor response rate measured by breast MRI.

Percent change in tumor volume from baseline after 2 months of niraparib treatment, measured in both MRI and ultrasound will be summarized using descriptive statistics.

Clinical response (i.e., completed response, partial response, stable response, progressive disease, and not evaluable) based on MRI and ultrasound will be also summarized using frequency distribution.

The above efficacy data, associated lesion assessments, new lesion assessment, and clinical response on primary lesion based on MRI and ultrasound will be provided in listings.

7.4.3 Subgroup Analyses of Efficacy Data

In order to estimate of the preliminary antitumor activity of niraparib BRCAmut TNBC patients and BRCAmut HR+ patients, all the summaries and analyses for primary and secondary efficacy data will be repeated for the following subgroups:

- TNBC patients -- TNBC is defined as estrogen receptor negative [ER-], progesterone receptor negative [PR-], and HER2-
- HR+ patients -- HR+ is defined as HER2- with either estrogen receptor positive [ER+] or progesterone receptor positive [PR +]

7.5 Analysis of Pharmacokinetic Data

A separate PK analysis plan will detail the analyses of PK samples of niraparib.

7.6 Analysis of Exploratory Efficacy Endpoints

A separate analysis plan will detail the analyses of exploratory efficacy endpoints except for estimate of the preliminary antitumor activity of niraparib BRCAmut TNBC patients and BRCAmut HR+ patients.

7.7 Analysis of Safety Data

7.7.1 Adverse Events

Adverse events will be classified into a standardized terminology MedDRA system organ classifications (SOC) and preferred terms (PT). Severity of AEs will be assessed by investigators according to CTCAE (v4.03).

A treatment-emergent AE (TEAE) will be defined as any new AE that begins, or any preexisting condition that worsens in severity after the first dose of study treatment.

The number and percentage of patients who experienced an AE will be summarized. The denominator for calculating the percentages will be based on the number of patients in the safety population.

The following types of summaries will be provided:

1. Overview of TEAEs
2. TEAEs by SOC and PT
3. TEAEs by SOC, PT, and Maximum CTCAE toxicity grade
4. TEAEs by PT in descending frequency
5. Related TEAEs by SOC and PT (Niraparib related and procedure related will be provided separately)
6. Related TEAEs by SOC, PT and Maximum CTCAE grade (Niraparib related and procedure related will be provided separately)
7. Related TEAEs by PT in descending frequency (Niraparib related and procedure related will be provided separately)
8. Serious TEAEs by SOC and PT
9. Related Serious TEAEs by SOC and PT (Niraparib related and procedure related will be provided separately)
10. CTCAE Grade >=3 TEAEs by SOC, PT, and Maximum CTCAE grade
11. Related CTCAE Grade >=3 TEAEs by SOC and PT (Niraparib related and procedure related will be provided separately)
12. TEAEs leading to Niraparib interruption by SOC and PT
13. TEAEs leading to Niraparib reduction by SOC and PT
14. TEAEs leading to Niraparib discontinuation by SOC and PT

15. TEAEs leading to death by SOC and PT
16. Treatment emergent AEs of special interest (AESI) by AESI category and PT: AESI categories are the following
    - Myelodysplastic Syndromes (MDS) and Acute Myeloid Leukemia (AML)
    - Secondary cancers (new malignancies [other than MDS or AML])
    - Pneumonitis
    - Embryo-fetal toxicity
17. Related Treatment emergent AESI by AESI category and PT ((Niraparib related and procedure related will be provided separately)
18. Non-serious TEAEs ⩾5% (required by Clinicaltrials.gov)

If a preferred term or system organ class 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 preferred term, only the most severe preferred term for each patient will be included.
- For a given system organ class, only the most severe system organ class for each patient will be included.

Similarly, in tabulation by relationship,

- For a given preferred term, the most closely related preferred term to the study drug for each patient will be included.
- For a given system organ class, the most closely related system organ class to the study drug for each patient will be included.

All AEs will be provided in a data listing.

7.7.2 Study Drug Exposure and Compliance

The following study drug exposure and compliance parameters will be summarized:

- Duration of niraparib exposure in months defined as

$$\frac{\text{Date of last dose of niraparib} - \text{Date of first dose of niraparib} + 1}{30.4375}$$

- Number of cycles initiated as continuous variable
- Number of cycles initiated as a categorical variable (1 cycle, 2 cycles, etc.)
- Number of patients with at least one dose interruption
- Number of patients with at least one dose reduction

- Number of patients with at least one missed dose
- Cumulative niraparib dosage (mg) received defined as sum of all niraparib dose received
- Actual dose intensity (mg/day) for niraparib defined as sum of the doses actually received divided by duration of niraparib exposure in days:

$$\frac{\text{Cumulative niraparib dosage (mg) received}}{\text{Duration of niraparib exposure (Days)}}$$

- Intended dose intensity (mg/day) for niraparib defined as sum of planned doses divided by duration of niraparib exposure in days

$$\frac{\text{Sum of planned niraparib doses (mg)}}{\text{Duration of niraparib exposure (Days)}}$$

- Relative dose intensity (%) for niraparib defined as:

$$\frac{\text{Actual dose intensity}}{\text{Intended dose intensity}} \times 100\%$$

Study drug exposure and compliance parameters will be summarized using descriptive statistics. Details of study drug administration, dose modifications and duration of exposure will be listed.

7.7.3 Clinical Laboratory Evaluations

Clinical laboratory assessments (CBC and serum chemistry) will be summarized by visit in descriptive nature. Descriptive statistics will be provided for continuous laboratory data and associated change from baseline. Frequency distribution will be provided for categorical laboratory.

The worst toxicity grades for selected laboratory tests as listed in Appendix B (Table 4) will be determined for each patient based on worst abnormal high and abnormal low lab values. The shift table from baseline CTCAE grade to the worst NCI CTC grade will be provided. Laboratory measurements that are within their institutional limits of normal and are not graded as 1-4, per the CTCAE, will be summarized as "Grade 0," which is defined as normal. Additionally, if a lab parameter is graded in both directions (e.g. glucose: hyperglycemia and hypoglycemia), then low direction toxicity grades at baseline and post baseline will be set to 0 when the variables are derived for summarizing high direction toxicity, and vice versa. Hyperglycemia will only be coded to grades ≥ 3 using non-fasting glucose and therefore will not be included in shift tables.

For shift table from baseline to post-baseline visit, the denominators for calculating the percentages will be based on the number of patients with non-missing values at both baseline and post-baseline analysis visit in the Safety population.

Liver function tests post baseline will be summarized by the following categories:

- ALT ⩾ 3×ULN, ALT ⩾ 5×ULN, ALT ⩾ 10×ULN, ALT ⩾ 20×ULN
- AST ⩾ 3×ULN, AST ⩾ 5×ULN, AST ⩾ 10×ULN, AST ⩾ 20×ULN
- (ALT or AST) ⩾ 3×ULN, (ALT or AST) ⩾ 5×ULN, (ALT or AST) ⩾ 10×ULN, (ALT or AST) ⩾ 20×ULN
- Total bilirubin ⩾ 2×ULN
- Concurrent ALT ⩾ 3×ULN and total bilirubin ⩾ 2×ULN
- Concurrent AST ⩾ 3×ULN and total bilirubin ⩾ 2×ULN
- Concurrent (ALT or AST) ⩾ 3×ULN and total bilirubin ⩾ 2×ULN
- Concurrent (ALT or AST) ⩾ 3×ULN and total bilirubin ⩾ 2×ULN and ALP > 2×ULN
- Potential Hy's law: Concurrent (ALT or AST) ⩾ 3×ULN and total bilirubin ⩾ 2×ULN and ALP ⩽ 2×ULN or missing

Concurrent measurements are those occurring on the same date.

Urinalysis is only collected at screening. The data will be provided in a listing. Pregnancy test data, if available, will also be provided in data listings.

7.7.4 Vital Signs

Vital signs (systolic and diastolic blood pressure, pulse, temperature, and weight) will be summarized by visit. Actual values and changes from baseline will be summarized at each visit.

Furthermore, the maximum increase, maximum decrease, and maximum change/magnitude from baseline will be summarized.

Baseline is defined as the last observation prior to start of the first dose of study drug(s).

7.7.5 Electrocardiogram

Electrocardiogram is only collected at screening. Therefore, ECG results will be provided in a data listing only.

7.7.6 Physical Examinations

Physical examinations and physical breast examinations will be provided in data listings only.

7.7.7 ECOG Performance Status

Shifts of ECOG performance status from baseline to the end of treatment will present frequency distribution for each category. The denominators for calculating the percentages will be based on the number of patients with non-missing baseline and post-baseline values.

Details on ECOG status will be provided in a data listing.

8 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

As a general rule, missing data values are not imputed unless otherwise specified below and, in presentation of categorical variables, unknown and missing data may be presented as a separate category in some case and the denominator will include unknown or missing values as appropriate.

8.1 Definition of Baseline

For all evaluations unless otherwise noted, baseline is defined as the most recent measurement prior to 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.

8.2 Analysis Visit Window

For safety parameters excluding clinical laboratory data, measurements collected from unscheduled visits will not be included in the by-visit summary tables but will be included in the listings.

8.3 Efficacy Data Handling

See Section 4.1.1 and 4.1.2 of the SAP.

8.4 Safety Data Handling

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

8.4.1 Handling of Repeated Clinical Laboratory Tests

The last repeat of laboratory results will be used in the summary tables for that visit. All the laboratory test results (original test results and repeated results) will be included in the data listings.

8.4.2 Handling of Partial Dates for AEs

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 study treatment. In this case, the onset date will be assumed to be the date of treatment.
- If the onset day and month are both missing, the month and day 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 set to the day of treatment to conservatively report the event as treatment-emergent.
- A completely missing onset date will be set 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.

8.4.3 Handling of Partial Dates for Medications

A medication with a completely missing start date will be considered a prior medication. A medication with a completely missing stop date will be considered a concomitant medication.

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.

9 REFERENCE

10 APPENDICE

Appendix A. Disease Assessment Criteria

Response will be assessed by imaging tests (ultrasound and MRI). Disease assessment is to be determined by changes in the tumor volume, calculated as length × width × height × π)/6. While all measurable lesions will be followed in cases multifocal or multicentric disease, only the largest or primary lesion will be used for assessing disease status as follows:

- **Clinical complete response (CR)**

  Complete disappearance of all tumor signs in the breast as assessed by imaging test. The response of the axillary nodes is not to be considered.

- **Clinical partial response (PR)**

  Reduction in the tumor volume of the primary tumor size by 30% or more assessed by palpation or imaging test. In patients with multifocal or multicentric disease, the lesion with the largest volume should be chosen for follow-up. The response of the axillary nodes is not to be considered.

- **Clinical stable disease (SD)**

  No significant change in tumor volume during treatment. This category includes no change, an estimated reduction of the tumor volume of the primary lesion by less than 30%, or an estimated increase in the size of the tumor volume of less than 20% measured imaging test.

- **Clinical progressive disease (cPD)**

  Development of new, previously undetected lesions, or an estimated increase in the size of the primary lesion by 20% or more.

Appendix B. Common Terminology Criteria for Adverse Events v4.03 (CTCAE)

Table 4: Common Terminology Criteria for Adverse Events v4.03 (CTCAE)

Lab Test	Std. Unit	CTCAE v4.0 SOC	CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin	g/L	Blood and lymphatic system disorders	Anemia	<LLN - 100 g/L	<100 – 80 g/L	<80 g/L	-
aPTT	sec	Investigations	Activated partial thromboplastin time prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN	-
ALT	U/L	Investigations	Alanine aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
ALP	U/L	Investigations	Alkaline phosphatase increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
AST	U/L	Investigations	Aspartate aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Bilirubin	umol/L	Investigations	Blood bilirubin increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN
CD4	10e9/L	Investigations	CD4 lymphocytes decreased	<LLN - 0.5 x 10e9 /L	<0.5 - 0.2 x 10e9 /L	<0.2 x 0.05 - 10e9 /L	<0.05 x 10e9 /L
Cholesterol	mmol/L	Investigations	Cholesterol high	>ULN - 7.75 mmol/L	>7.75 - 10.34 mmol/L	>10.34 - 12.92 mmol/L	>12.92 mmol/L
CPK (creatinine phosphor-kinase)	-	Investigations	CPK increased	>ULN - 2.5 x ULN	>2.5 - 5 x ULN	>5 - 10 x ULN	>10 x ULN
Creatinine	umol/L	Investigations	Creatinine increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 6.0 x ULN	>6.0 x ULN
Fibrinogen	-	Investigations	Fibrinogen decreased	<1.0 - 0.75 x LLN	<0.75 - 0.5 x LLN	<0.5 - 0.25 x LLN	<0.25 x LLN
GGT (gamma-glutamyl-transferase)	-	Investigations	GGT increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
INR	-	Investigations	INR increased	>1 - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN	-
Lipase	-	Investigations	Lipase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 - 5.0 x ULN	>5.0 x ULN
Lymphocytes	10e9/L	Investigations	Lymphocyte count decreased	<LLN - 0.8 x 10e9/L	<0.8 - 0.5 x 10e9 /L	<0.5 - 0.2 x 10e9 /L	<0.2 x 10e9 /L
Neutrophils	10e9/L	Investigations	Neutrophil count decreased	<LLN - 1.5 x 10e9 /L	<1.5 - 1.0 x 10e9 /L	<1.0 - 0.5 x 10e9 /L	<0.5 x 10e9 /L

Table 4: Common Terminology Criteria for Adverse Events v4.03 (CTCAE)

Lab Test	Std. Unit	CTCAE v4.0 SOC	CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4
Platelets	10e9/L	Investigations	Platelet count decreased	<LLN - 75.0 x 10e9 /L	<75.0 - 50.0 x 10e9 /L	<50.0 - 25.0 x 10e9 /L	<25.0 x 10e9 /L
Amylase	-	Investigations	Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 - 5.0 x ULN	>5.0 x ULN
Leukocytes	10e9/L	Investigations	White blood cell decreased	<LLN - 3.0 x 10e9 /L	<3.0 - 2.0 x 10e9 /L	<2.0 - 1.0 x 10e9 /L	<1.0 x 10e9 /L
Calcium (corrected)	mmol/L	Metabolism and nutrition disorders	Hypercalcemia	>ULN - 2.9 mmol/L	>2.9 - 3.1 mmol/L	>3.1 - 3.4 mmol/L	>3.4 mmol/L
Glucose	mmol/L	Metabolism and nutrition disorders	Hyperglycemia	Fasting glucose >ULN - 8.9 mmol/L	Fasting glucose >8.9 - 13.9 mmol/L	>13.9 - 27.8 mmol/L	>27.8 mmol/L
Potassium	mmol/L	Metabolism and nutrition disorders	Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L	>7.0 mmol/L
Magnesium	mmol/L	Metabolism and nutrition disorders	Hypermagnesemia	>ULN - 1.23 mmol/L	-	>1.23 - 3.30 mmol/L	>3.30 mmol/L
Sodium	mmol/L	Metabolism and nutrition disorders	Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L	>160 mmol/L
Triglyceride	mmol/L	Metabolism and nutrition disorders	Hypertriglyceridemia	1.71 - 3.42 mmol/L	>3.42 - 5.7 mmol/L	>5.7 - 11.4 mmol/L	>11.4 mmol/L
Albumin	g/L	Metabolism and nutrition disorders	Hypoalbuminemia	<LLN - 30 g/L	<30 - 20 g/L	<20 g/L	-
Calcium (corrected)	mmol/L	Metabolism and nutrition disorders	Hypocalcemia	<LLN - 2.0 mmol/L	<2.0 - 1.75 mmol/L	<1.75 - 1.5 mmol/L	<1.5 mmol/L
Glucose	mmol/L	Metabolism and nutrition disorders	Hypoglycemia	<LLN - 3.0 mmol/L	<3.0 - 2.2 mmol/L	<2.2 - 1.7 mmol/L	<1.7 mmol/L
Potassium	mmol/L	Metabolism and nutrition disorders	Hypokalemia	<LLN - 3.0 mmol/L	<LLN - 3.0 mmol/L	<3.0 - 2.5 mmol/L	<2.5 mmol/L
Magnesium	mmol/L	Metabolism and nutrition disorders	Hypomagnesemia	<LLN - 0.5 mmol/L	<0.5 - 0.4 mmol/L	<0.4 - 0.3 mmol/L	<0.3 mmol/L
Sodium	mmol/L	Metabolism and nutrition disorders	Hyponatremia	<LLN - 130 mmol/L	-	<130 - 120 mmol/L	<120 mmol/L
Phosphate	mmol/L	Metabolism and nutrition disorders	Hypophosphatemia	<LLN - 0.8 mmol/L	<0.8 - 0.6 mmol/L	<0.6 - 0.3 mmol/L	<0.3 mmol/L

Appendix C. TNM Definitions

Primary tumor (T):

- TX: Primary tumor cannot be assessed.
- T0: No evidence of primary tumor.
- Tis: Carcinoma in situ (DCIS, LCIS, or Paget disease of the nipple with no associated tumor mass)
- T1: Tumor ⩽20 mm in greatest dimension.
- T2: Tumor >20 mm but ≤50 mm in greatest dimension.
- T3: Tumor >50 mm in greatest dimension.
- T4: Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules)

Regional lymph nodes (N):

- NX: Regional lymph nodes cannot be assessed (e.g., previously removed)
- N0: No regional lymph node metastases
- N1: Metastases to movable ipsilateral level I, II axillary lymph node(s).
- N1mi: Micrometastases (>0.2 mm and/or >200 cells but none >2.0 mm).
- N2: Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted OR Metastases in clinically detected ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastases.
- N3: Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement OR Metastases in clinically detected ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph node metastases OR Metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement.

Distant metastasis (M):

- MX: Presence of distant metastases cannot be assessed.
- M0: No clinical or radiographic evidence of distant metastases. No distant metastasis
- M1: Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven >0.2 mm.

Appendix D. AJCC Stage Groupings

Stage TNM

- Stage 0 Tis, N0, M0
- Stage I T1, N0, M0 / T0 or T1, N1mi, M0
- Stage IIA T0 or T1, N1 (but not N1mi), M0 / T2, N0, M0
- Stage IIB T2, N1, M0 / T3, N0, M0
- Stage IIIA T0 to T2, N2, M0 / T3, N1 or N2, M0
- Stage IIIB T4, N0 to N2, M0
- Stage IIIC any T, N3, M0
- Stage IV any T, any N, M1
- UNKNOWN Unknown