NIRAPARIB

3000-01-005

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

Sponsor:	TESARO, Inc. 1000 Winter Street Waltham, MA 02451 PPD TESARO UK Limited 55 Baker Street London W1U 7EU United Kingdom PPD
Medical Monitor:	PPD, MD Sr. Medical Director TESARO PPD
Sponsor Protocol No.:	3000-01-005
IND No:	117580
Study Drug Names:	Niraparib capsules
Development Phase:	Pilot Study
Date of Original Protocol:	16 September 2017
Date of Amendment 1:	01 August 2018
Version of Protocol:	2.0

The study will be conducted according to the protocol and in compliance with Good Clinical Practice (GCP), with the Declaration of Helsinki, and with other applicable regulatory requirements.

SPONSOR SIGNATURE PAGE

Declaration of Sponsor or Responsible Medical Officer

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

This study protocol was subjected to critical review and has been approved by the Sponsor. The information it contains is consistent with the current risk/benefit evaluation of the investigational products as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki and the guidelines on Good Clinical Practice.

PPD

PPD , MD
Senior Medical Director
TESARO

01 Aug 2018
Date

INVESTIGATOR'S AGREEMENT

Declaration of the Principal Investigator

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

I have read this study protocol, including all appendices. By signing this protocol, I agree to conduct the clinical study, following approval by an Independent Ethics Committee/Institutional Review Board, in accordance with the study protocol, the current International Council for Harmonisation Guideline for Good Clinical Practice, and applicable regulatory requirements. I will ensure that all personnel involved in the study under my direction will be informed about the contents of this study protocol and will receive all necessary instructions for performing the study according to the study protocol.

_____

Printed Name of Investigator

_____

Institution

_____

Signature of Investigator

_____

Date

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone Number
Clinical Study Leader	PPD, MD	TESARO 1000 Winter Street Waltham, MA 02451 PPD

2. SYNOPSIS

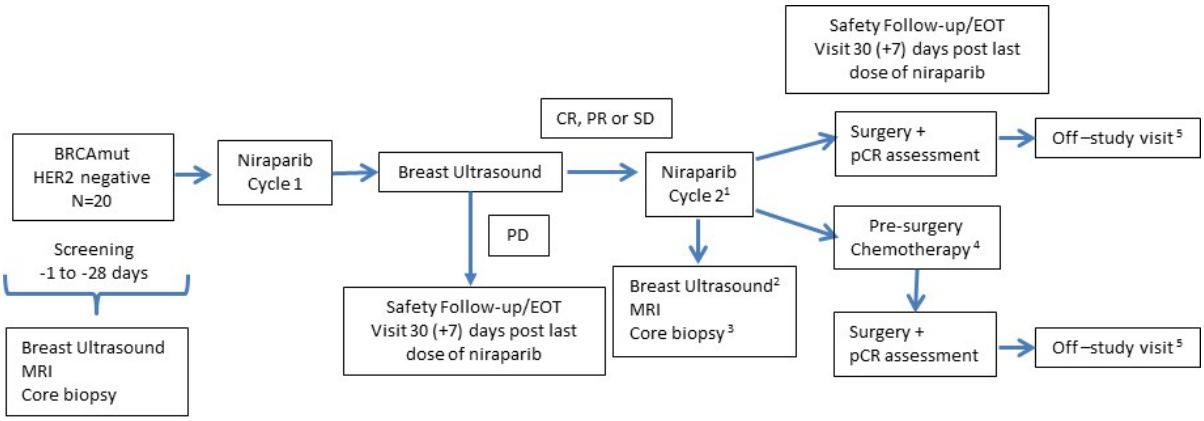
<table>
<tr><td colspan="2">Name of Sponsor/Company: TESARO</td></tr>
<tr><td colspan="2">Name of Investigational Product: Niraparib</td></tr>
<tr><td colspan="2">Name of Active Ingredient: Niraparib</td></tr>
<tr><td colspan="2">Title of Study: An Open-Label, Single-arm Pilot Study Evaluating the Antitumor Activity and Safety of Niraparib as Neoadjuvant Treatment in Localized, HER2-negative, BRCA-mutant Breast Cancer Patients</td></tr>
<tr><td colspan="2">Study center(s): North America (multicenter)</td></tr>
<tr><td>Studied period (years):
Estimated date first patient enrolled: April 2018
Estimated date last patient completed: TBD</td><td>Phase of development:
Pilot Study</td></tr>
<tr><td colspan="2">Objectives:
Primary:
• 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, human epidermal growth factor receptor 2 (HER2)-negative, breast cancer susceptibility gene (BRCA) mutant (BRCAmut) breast cancer patients.
Secondary:
• To evaluate the preliminary antitumor activity of niraparib assessed by:
– Presence of pathological complete response (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 the current version of the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.03 criteria
Exploratory:
• 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 patients
• To evaluate pharmacodynamic inhibition of PARP activity in the tumor</td></tr>
</table>

- To explore molecular biomarkers related to disease biology or response to treatment using tumor tissue or liquid biopsy approaches (e.g. ctDNA)

Methodology:

This is an open-label, single-arm pilot study evaluating the antitumor activity and safety of niraparib as neoadjuvant therapy in patients with HER2-negative and *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.

Study Schema



[1]Patients may receive up to 6 months of niraparib (see Section 7).
[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.

Breast magnetic resonance imaging (MRI), breast ultrasound, and tumor core biopsy will be performed at the Screening (-28 to -1 Day 1).

Patients will receive niraparib (200 mg orally [PO]) treatment daily for 28 days (Cycle 1) and then will undergo breast ultrasound at the end of Cycle 1 on Day 28:

- If breast ultrasound shows disease progression defined as an increase in tumor volume by greater than 20% by Investigator assessment, the patient will discontinue the study. If breast ultrasound shows complete response, partial response, or stable disease by Investigator assessment, the patient will continue niraparib treatment 200 mg PO for an additional cycle (Cycle 2). Patients may receive up to 6 months of niraparib treatment if, in the opinion of the Investigator and Sponsor, and agreed upon by the Sponsor, the patient would benefit from additional treatment.

A breast MRI and breast ultrasound will be performed at the end of Cycle 2. The investigational team will determine if the patient will proceed to surgery or to neoadjuvant chemotherapy.

A core biopsy will be performed at the end of Cycle 2, which should occur within 24 hours of the last dose of niraparib. Niraparib treatment may be extended up to an additional 7 days after Cycle 2 Day 28 to allow for scheduling of surgery or the core biopsy:

- For those patients proceeding directly to surgery at the end of Cycle 2, a surgical biopsy may be obtained at the time of surgery provided that surgery occurs within 24 hours of the last dose of niraparib on Cycle 2 Day 28 (+7 days).
- For all other patients, provided that their tumors are amenable to biopsy, a core biopsy should be obtained within 24 hours of the last dose of niraparib on Cycle 2 Day 28 (+7 days). The biopsy should be performed after the MRI and ultrasound and prior to any subsequent anticancer therapy.

At the completion of all neoadjuvant therapy, patients will proceed to surgery and/or other local treatment as deemed appropriate by the investigator. For those patients who receive neoadjuvant therapy (niraparib alone or niraparib followed by chemotherapy), a pCR assessment will be made at the time of surgery.

Patients shall discontinue treatment in case of unacceptable toxicity or withdrawal of consent.

All adverse events (AEs) will be collected and recorded for each patient from the day of signing the informed consent form until 30 days after last study drug administration.

Selected non-serious AEs and serious adverse events (SAEs) are also known as adverse events of special interest (AESI) and must be recorded as such on the electronic case report form (eCRF) and reported within 24 hours to the Sponsor as soon as the Investigator becomes aware of them.

SAEs are required to be captured through 90 days after the last dose of study drug (or to a minimum of 30 days post treatment if the patient starts alternate anticancer therapy). All SAEs assessed by the Investigator as related to the study drug and AESIs will be collected and reported until study closeout. Any pregnancies that occur up to and including 180 days post-treatment will be reported. Pregnancies occurring more than 180 days after last dose, with an associated SAE (considered causally related to the study drug by the Investigator) will follow the SAE reporting requirements.

All AEs and SAEs experienced by a patient, irrespective of the suspected causality, will be monitored until the AE or SAE has resolved, until abnormal laboratory values have returned to baseline or normalized, until there is a satisfactory explanation for the changes observed, until the patient is lost to follow-up, or until the patient has died.

Number of patients (planned): Approximately 20

Diagnosis and main criteria for inclusion:

1. Patients age ≥18 years old
2. Patients with a deleterious or suspected deleterious *BRCA1* or *BRCA2* mutation (germline or somatic) may be enrolled into the study based on either local or central laboratory testing of *BRCA* status
3. Histologically-confirmed HER2-negative localized breast cancer by core biopsy.

4. Primary operable, non-metastatic invasive carcinoma of the breast, confirmed histologically by core biopsy. Fine-needle aspiration is not sufficient. Incisional biopsy is not allowed. In patients with multifocal and/or multicentric, the largest lesion should be measured. Both unilateral and bilateral breast cancer are allowed.
5. Primary tumor size ≥1 cm
6. Measurable disease by breast ultrasound and MRI
7. Eastern Cooperative Oncology Group performance status of 0 or 1
8. Adequate organ function, defined as follows:

Note: Complete blood count should be obtained without transfusion or receipt of colony stimulating factors within 4 weeks prior to obtaining a sample.

a. Absolute neutrophil count (ANC) ≥1,500/μL

b. Platelets ≥100,000/μL

c. Hemoglobin ≥9 g/dL

d. Serum creatinine ≤1.5 x upper limit of normal (ULN) or calculated creatinine clearance ≥ 50 mL/min using Cockcroft-Gault equation

e. Total bilirubin ≤1.5× ULN except in patients with Gilbert's syndrome. Patients with Gilbert's syndrome may enroll if direct bilirubin ≤1.5 × ULN of the direct bilirubin

f. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 x ULN

9. Patient must have recovered to Grade 1 toxicity from prior cancer therapy (a patient with Grade 2 neuropathy or Grade 2 alopecia is an exception to this criterion and may qualify for this study).
10. Able to take oral medications
11. Patient meets the following criteria:

a. Female patient (of childbearing potential) is not breastfeeding, has a negative serum pregnancy test within 72 hours prior to taking study drug, and agrees to abstain from activities that could result in pregnancy from the Screening through 180 days after the last dose of study drug, or is of nonchildbearing potential.

Note: A urine pregnancy test may be performed if the serum pregnancy test is not available before dosing.

b. Female patient is of nonchildbearing potential (other than medical reasons) as defined by the following:
   i. ≥45 years of age and has not had menses for >1 year.
   ii. Amenorrheic for <2 years without a hysterectomy and oophorectomy and a follicle-stimulating hormone value in the postmenopausal range upon the Screening evaluation.
   iii. Has undergone post hysterectomy, bilateral oophorectomy, or tubal ligation. Documented hysterectomy, oophorectomy or tubal ligation must be confirmed in the medical records, otherwise the patient must be willing to use 2 adequate barrier methods throughout the study starting from the Screening visit through 180 days after the last dose of study drug. Information must be captured appropriately within the site's source documents.

c. Male patient agrees to use an effective method of contraception (please see Section 9.2.2 for a list of acceptable birth control methods) starting with the first dose of study therapy through 120 days after the last dose of study therapy

Note: Abstinence is acceptable if this is the established and preferred contraception method for the patient.

12. Able to understand the study procedures and agree to participate in the study by providing written informed consent

Exclusion Criteria:

1. Prior anti-cancer therapies for current malignancy
2. Known evidence of distant metastasis. Staging studies are not required.

   The decision to pursue staging studies is at the discretion of the treating clinician, based on the patient's clinical and pathologic findings consistent with standard guidelines.
3. Known hypersensitivity to the components of niraparib components or their formulation excipients
4. Major surgery within 3 weeks of starting the study or patient has not recovered from any effects of any major surgery
5. Poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 90 days) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, uncontrolled hypertension, active uncontrolled coagulopathy, bleeding disorder, or any psychiatric disorder that prohibits obtaining informed consent
6. History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the patient's participation for the full duration of the study drug, or is not in the best interest of the patient to participate
7. Patient is pregnant or breastfeeding, or expecting to conceive children within the projected duration of the study drug or within the 180-day period after the last dose of study drug
8. Immunocompromised patients (Note: patients with splenectomy are allowed)
9. Known active hepatic disease (ie, Hepatitis B or C)
10. Prior treatment with a known PARP inhibitor
11. Other active malignancy that warrants systemic therapy
12. Known history of myelodysplastic syndromes or acute myeloid leukemia

Investigational product, dosage and mode of administration:

Niraparib (100 mg niraparib capsules) will be supplied and starting dose will be 200 mg. Study drug will be administered PO daily throughout 28 days for 2 cycles, with the potential for an additional 4 cycles (maximum total of 6 cycles), at the assigned dose and schedule.

Duration of treatment:
Approximately 56 days.

Reference therapy, dosage and mode of administration:
Not applicable

Criteria for evaluation:

Efficacy:

The primary efficacy endpoint is:

- Tumor response rate based on the change in tumor volume as measured by breast MRI; a response is considered ≥30% reduction of tumor volume from baseline after 2 months of niraparib treatment. Tumor volume will be calculated as (length × width × height × π)/6.

The secondary efficacy endpoints are:

- pCR rate: pCR is defined as *ypT0/Tis ypN0* by receipt of pre-operative chemotherapy (Yes vs. No). Pathological complete response (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[1]).
- Tumor response rate based on the change in tumor volume as measured by breast ultrasound; a response is considered ≥30% reduction of tumor volume from baseline after 2 months of niraparib treatment. 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.
- 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 exploratory endpoints are:

- 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 *BRCA*mut TNBC patients and in *BRCA*mut 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

Safety:

- Safety by toxicity grades as defined by the NCI-CTCAE v.4.03 criteria
- Incidence of treatment-emergent AEs (TEAEs)
- Changes in clinical laboratory parameters (hematology, chemistry)
- Vital signs
- Physical examinations
- Usage of concomitant medications

Statistical methods:

No formal sample size calculation is 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.

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

The safety population includes all patients who received any dose of study medication. The safety population will be the primary analysis population for the safety analyses.

The efficacy evaluable population includes all patients who completed 2 cycles of treatment. The efficacy evaluable population will be the primary analysis population for the efficacy analyses.

No formal statistical testing will be done for this study. Data will be summarized in a descriptive nature. Categorical variables will be summarized by frequency distributions (number and percentage of patients). Continuous variables will be summarized by the mean, standard deviation, median, minimum, maximum, first quartile and third quartile.

Tumor response rate will be tabulated together with its 95% binomial exact confidence interval (CI). The change in tumor volume from baseline will be summarized using descriptive statistics. Data from patients who received neoadjuvant niraparib only will be analyzed separately from those who received neoadjuvant niraparib followed by neoadjuvant chemotherapy.

Summary statistics will be provided for safety endpoints including TEAEs, clinical laboratory evaluations (hematology, chemistry, and urinalysis), vital signs, electrocardiograms, physical examinations, and use of concomitant medications.

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 2: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE	adverse event
AESI	adverse events of special interest
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BCSS	breast cancer-specific survival
BRCA	breast cancer susceptibility gene
*BRCA*mut	breast cancer susceptibility gene mutant
C1	cohort 1
C2	cohort 2
CBC	complete blood count
CI	confidence interval
CR	complete response
ctDNA	circulating tumor DNA
CYP	cytochrome P450
DFS	disease free survival
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EFS	event-free survival
EOT	end of treatment
FFPE	formalin-fixed paraffin embedded
g*BRCA*	germline breast cancer susceptibility gene
GCP	Good Clinical Practice
HER2	Human epidermal growth factor receptor 2
HR	hazard ratio
HRD	homologous recombination deficiency

Abbreviation or Specialist Term	Explanation
IC_{50}	half maximal inhibitory concentration of control
IC_{90}	90% inhibitory concentration of control
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LOH	loss of heterozygosity
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NBF	neutral buffered formalin
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
ORR	objective response rate
OS	overall survival
PARP	poly(ADP-ribose) polymerase
pCR	pathological complete response
PD	pharmacodynamic
PDX	patient-derived tumor graft
PFS	progression free survival
PI	Principal Investigator The Investigator who leads the study conduct at an individual study center. Every study center has a principal Investigator.
PK	pharmacokinetics
PO	oral(ly)
PR	partial response
QD	once daily
QTc	corrected QT interval
SAE	serious adverse event
SD	stable disease
TEAE	treatment-emergent adverse event
TNBC	triple-negative breast cancer
US	United States of America
ULN	upper limit of normal

5. INTRODUCTION

5.1. Background

5.1.1. Breast Cancer

Breast cancer is the most common cancer in women worldwide, with nearly 1.7 million new cases diagnosed in 2012 (second most common cancer overall). This represents about 12% of all new cancer cases and 25% of all cancers in women.[2] In the United States of America (U.S.), approximately 1 in 8 women (about 12%) will develop invasive breast cancer over the course of her lifetime. In the U.S. alone, it is estimated that there will be 252,710 new cases of female breast cancer and an estimated 40,610 people will die of this disease in 2017.[3] In Europe, more than 464,000 new cases of breast cancer were estimated to have been diagnosed in 2012.[4]

Approximately 20 to 25 % of hereditary breast cancers and 5 to 10% of all breast cancers are associated with pathogenic germline alterations in breast cancer susceptibility gene (*BRCA)1* and *BRCA2*.[5,6] Women with *BRCA* mutations have a lifetime risk of developing breast cancer of 45 to 75%.[7-9] *BRCA*mut breast cancer is characterized by more aggressive phenotype than sporadic breast cancer, with *BRCA1*-mutated breast cancer being more frequently high grade and triple negative, and *BRCA2*-mutated breast cancer being on average of higher histological grade than sporadic cases.[7,10,11] *BRCA1* mutation carriers have worse overall survival (OS) than *BRCA*-wildtype cases (hazard ratio [HR]: 1.30, 95% CI: 1.11–1.52) and worse breast cancer-specific survival (BCSS) than sporadic/*BRCA*-wildtype cases among patients with stage I–III breast cancer (HR 1.45, 95% CI: 1.01–2.07). *BRCA2* mutation carriers have worse BCSS than sporadic/*BRCA*-wildtype cases (HR 1.29, 95% CI: 1.03–1.62), although they have similar OS. Among Ashkenazi Jewish women, *BRCA1/2* mutation carriers presented higher risk of death from breast cancer (HR 1.44, 95% CI: 1.05–1.97) and of distant metastases (HR 1.82, 95% CI: 1.05–3.16) than sporadic/*BRCA*-wildtype patients.[12]

BRCA1/*2*-mutant cells are hypersensitive to inactivation of poly (ADP-ribose) polymerase 1 (PARP-1), garnering great interest in the treatment of breast cancer patients with *BRCA1*/*2*-mutant disease via PARP inhibition. The PARP inhibitor olaparib was assessed for efficacy and safety in women with *BRCA1* or *BRCA2*-mutant advanced breast cancer.[13] In this proof-of concept phase 2 study, women were assigned to two sequential cohorts, the first cohort (n = 27) was given continuous oral olaparib at the maximum tolerated dose (400 mg twice daily), and the second (n = 27) was given a lower dose (100 mg twice daily). The primary objective was objective response rate (ORR); ORR was 11 (41%) of 27 patients (95% CI 25–59) in the cohort assigned to 400 mg twice daily, and 6 (22%) of 27[3,12,14,15] in the cohort assigned to 100 mg twice daily. The results of this study provided proof of concept for PARP inhibition in *BRCA*mut breast cancers and shows a favorable therapeutic index for a novel targeted treatment strategy in patients with tumors that have genetic loss of function of *BRCA1*-associated or *BRCA2*-associated deoxyribonucleic acid (DNA) repair.

More recently, the ABRAZO study was initiated to investigate the use of PARP inhibitor talazoparib in patients with g*BRCA1*/*2* mutation previously exposed to platinum or multiple prior cytotoxic regimens (Turner et al 2017).[16] This study is a 2-cohort, 2-stage phase 2 study of talazoparib following platinum-based therapy (Cohort 1 [C1]) or ≥ 3 platinum-free cytotoxic-based regimens (Cohort 2 [C2]) in patients with locally advanced or metastatic breast

cancer and g*BRCA1/2* mutation. Five responses per cohort were required in ≤ 35 patients to progress to stage 2. The primary endpoint was confirmed ORR by independent radiology facility. As of Sep 2016, 84 patients had enrolled (C1, n = 49; C2, n = 35). Both cohorts proceeded to stage 2 before enrollment closed. Triple negative breast cancer (TNBC)/human epidermal growth factor receptor 2 (HER2)-positive (TNBC/HER2-positive) breast cancer incidence in C1 and C2 was 59%/41% and 17%/83%, respectively. ORR for *BRCA1*/*BRCA2* was 24%/34%, and ORR by for TNBC/HER2-positive was 26%/29%. Based on these data, the phase 3 EMBRACA trial was initiated to test the use of talazoparib versus physician's choice of treatment in g*BRCA1*/*2*-mutated metastatic breast cancer.

The efficacy and tolerability of the PARP inhibitor veliparib was tested in combination with carboplatin and paclitaxel versus placebo given with carboplatin and paclitaxel in patients with *BRCA1* or *BRCA2* mutations and metastatic breast cancer in the BROCADE study.[17] In this randomized, phase 2 study, 290 patients with *BRCA1* or *BRCA2* mutation were randomized to three arms: 97 were randomized to veliparib plus carboplatin and paclitaxel, 99 to placebo plus carboplatin and paclitaxel, and 94 to veliparib plus temozolomide. The overall response rate for the veliparib arm was 77.8%, compared with 61.3% for the placebo arm. The improvement in progression-free survival in the veliparib arm (14.1 vs 12.3 months) was not statistically significant. The trend to improved overall survival was also not statistically significant (28.3 vs 25.9 months). These results indicate that not all PARP inhibitors can be expected to be effective in the treatment of *BRCA1*/*2*-mutant breast cancer, thus requiring careful investigation for the optimal treatment of these patients in each setting.

Most recently and importantly, the benefit of treatment with olaparib was confirmed in the phase 3 OlympiAD study, which included 302 patients with HER2-negative metastatic breast cancer who harbored germline *BRCA1* or *BRCA2* mutations. Patients were randomized to olaparib (300 mg twice daily) or physician's choice of standard chemotherapy (capecitabine, vinorelbine, or eribulin). The primary endpoint of the trial was progression free survival (PFS) per a blinded independent review. Results showed a statistically-significant and clinically-meaningful improvement in PFS for patients treated with olaparib tablets compared to treatment with physician's choice of a standard of care chemotherapy. In addition to meeting its primary endpoint, the trial showed that patients treated with olaparib had a 42% reduction in risk of their disease worsening or death (HR 0.58; 95% CI 0.43-0.80; p=0.0009; median 7.0 vs 4.2 months) compared to those who received chemotherapy (capecitabine, vinorelbine, eribulin).[18] Secondary endpoints showed an improvement in time until second progression or death (PFS2) in the olaparib arm of the trial versus those treated with chemotherapy (HR 0.57; 95% CI: 0.40-0.83). In addition, the ORR was more than doubled, with 59.9% of patients in the olaparib arm showing response to treatment, compared to 28.8% of patients treated with chemotherapy. Notably, there was a lower incidence of grade ≥3 adverse events (AEs) in the olaparib arm compared to the chemotherapy arm (36.6% vs 50.5% respectively). This study establishes PARP inhibition with olaparib as effective in the treatment of *BRCA1*/*2*-mutant breast cancer.

Originally developed for patients with locally advanced breast cancer, neoadjuvant chemotherapy is now frequently administered to patients with operable breast cancers. The outcomes of neoadjuvant chemotherapy were demonstrated in a 2007 meta-analysis that included data from 5500 women participating in 1 of 14 trials reported between 1991 and 2001.[3]

Compared with adjuvant chemotherapy, neoadjuvant chemotherapy resulted in a reduction in the risk of having a modified radical mastectomy performed (hazard ratio [HR] 0.71, 95% CI 0.67-0.75), but equivalent OS (HR 0.98, 95% CI 0.87-1.09) and disease free survival (DFS) (HR 0.97, 95% CI 0.89-1.07). Among patients treated with neoadjuvant chemotherapy, a documented pathologic complete response (pCR) at surgery was prognostically significant in that these patients had significant improvements in both OS (HR 0.48, 95% CI 0.33-0.69) and DFS (HR 0.48, 95% CI 0.37-0.63) compared with patients with residual invasive disease.[14,15,19] These differences are more pronounced in patients with more proliferative breast cancer subtypes, including triple-negative breast cancer (TNBC; event-free survival [EFS] HR 0.24 for pCR versus not) and HER2-positive breast cancer (EFS HR 0.39 for pCR versus not).[15] Commonly used regimens for patients with HER2-negative disease include anthracycline-based regimens such as doxorubicin and cyclophosphamide followed or preceded by a taxane (docetaxel or paclitaxel) and nonanthracycline-containing regimens such as docetaxel and cyclophosphamide, amongst others.

In an effort to improve outcomes, additions to these agents, including antiangiogenesis agents have been investigated. The GeparQuinto phase 3 study was initiated in part to investigate subtype-specific treatment approaches for patients with HER2-negative primary breast cancer (group 1).[20] In this group, the rates of pCR after neoadjuvant chemotherapy with or without bevacizumab was evaluated. Results from this prespecified subgroup analyses suggested that the effect of bevacizumab derived mainly from patients with triple-negative breast cancer (odds ratio, 1.67). However, the test for interaction was not significant (P = 0.07) in this study, which was not powered to show these differential effects. In the National Surgical Adjuvant Breast and Bowel Project B-40 study a numerical but statistically nonsignificant increase in the rate of pCR was reported with the use of bevacizumab in the subgroup of 490 patients with triple-negative breast cancer.[21] In both studies, higher rates of bleeding, thromboembolic events, and postsurgical complications (early and late) were seen with the addition of bevacizumab therapy.

The use of PARP inhibitors has also been investigated in combination with chemotherapy in the neoadjuvant setting. Most recently, a pilot study of talazoparib for early-stage breast cancer patients with a *BRCA* mutation was initiated[22]. Thirteen patients were enrolled in initial stage of the study, *BRCA1*-mutant=10; *BRCA2*-mutant=3. Eight had hormone receptor negative and 4 had hormone receptor positive breast cancer, and 1 metaplastic. Two had clinical stage III, 9 had clinical stage II, and 2 had clinical stage I cancers. Decreases in tumor volume occurred in all 13 patients following 2 months of talazoparib monotherapy, with an average volume loss of 78% (range 30-98%). Talazoparib was well tolerated with no grade 4 toxicities and only one patient requiring dose reduction due to grade 3 neutropenia. Given the profound clinical response with only 2 months of therapy and favorable toxicity profile, the pilot study was discontinued early and an expansion cohort to estimate pathologic response to talazoparib alone with 4 to 6 months is underway. This small study provides early evidence of proof-of-concept in the treatment of *BRCA1/2*-mutant breast cancer with PARP inhibition.

5.1.1.1. Niraparib: Pre-Clinical Summary

Niraparib is a potent and selective PARP-1 and PARP-2 inhibitor with half maximal inhibitory concentration of control (IC_{50}) of 3.8 and 2.1 nM, respectively, and is at least 100-fold selective over other PARP-family members. Niraparib inhibits PARP activity stimulated as a result of

DNA damage caused by addition of hydrogen peroxide in various cell lines with an IC_{50} and a 90% inhibitory concentration of control (IC_{90}) of about 4 and 50 nM, respectively.[23]

Niraparib demonstrates selective anti-proliferative activity for cancer cell lines that have been silenced for *BRCA1* or *BRCA2* or carry *BRCA1* or *BRCA2* mutations as compared to their wild type counterparts. Niraparib demonstrates weak activity on normal human cells.

Niraparib displayed strong antitumor activity in in vivo studies with *BRCA1* mutant breast cancer (MDA-MB-436), *BRCA2* mutant pancreatic cancer, ataxia telangiectasia-mutant mantle cell lymphoma (GRANTA- 519), serous ovarian cancer (OVCAR3), and colorectal cancer (HT29 and DLD-1) xenograft models and with patient-derived Ewing's sarcoma mice models. Moreover, Murai et al demonstrated in 2012 that niraparib is the most potent amongst a series of 5 PARP inhibitors in trapping PARP.[24]

Nonclinical testing of niraparib did not indicate any untoward effects that would prevent clinical investigation in the human setting. Nonclinical pharmacology studies with niraparib have generated sufficient data to support its clinical evaluation as a monotherapy for patients with advanced/metastatic breast cancer with *BRCA* mutation.

Details of the nonclinical studies conducted with niraparib can be found in the current Investigator's Brochure.

5.1.1.2. Niraparib: Clinical Summary

Clinical studies have shown that PARP inhibitors are active in recurrent ovarian cancer.[25-31] PARP inhibition appears to be most active in patients with germline breast cancer susceptibility gene (g*BRCA*) mutation and in patients who are sensitive to platinum-containing therapy. However, clinical benefit has also been observed in g*BRCA* wild-type.[27-30] Maintenance treatment of high-grade serous ovarian cancer patients with recurrent platinum sensitivity showed that the PARP1/2 inhibitor niraparib significantly improved PFS in g*BRCA*mut patients (21 months for niraparib vs. 5.5 months for control). Furthermore, in the g*BRCA* wild-type population, significant improvement in PFS also was observed (9.3 months for niraparib versus 3.9 months for placebo, HR = 0.45, $p<0.0001$).[31,32] Zejula™ (niraparib) has been recently approved for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer. For more details, refer to Zejula label.[33]

There are 3 ongoing Phase 3 niraparib studies, Study PR-30-5010-C (BRAVO), Study PR-30-5017-C (PRIMA), and Study PR-30-5011-C (NOVA). There is also 1 ongoing Phase 1/2 study, Study 3000-PN162-01-001 (TOPACIO) and 1 ongoing Phase 2 study, Study PR-30-5020-C (QUADRA).

NOVA is a double-blind, placebo-controlled study in patients with platinum-sensitive ovarian cancer who have received at least 2 platinum-based regimens.[32] A total of 553 patients were categorized according to the presence or absence of a g*BRCA*mut (g*BRCA* cohort and non-g*BRCA* cohort) and the type of non-g*BRCA*mut, and were randomly assigned in a 2:1 ratio to receive niraparib (300 mg) or placebo once daily (QD). The primary endpoint was PFS. The study enrolled 203 patients in the g*BRCA*mut cohort and 350 patients in the non-g*BRCA*mut cohort. Among the 350 patients in the non-g*BRCA*mut cohort, 162 had tumors that were defined as HRD positive and 134 had tumors that were HRD negative. HRD status was not determined for 54 patients.

Demographic and baseline characteristics were well balanced. Table 3 shows the results for the PFS primary endpoint for each of the 3 primary efficacy populations (ie, g*BRCA*-mutant cohort, HRD positive cohort, and overall non-g*BRCA*mut cohort). In addition, median PFS in patients with HRD negative tumors was 6.9 months (95% CI: 5.6, 9.6) in the niraparib arm vs. 3.8 months (95% CI: 3.7, 5.6) in the placebo arm, with an HR of 0.58 (95% CI: 0.361, 0.922) (p=0.0226).

Table 3: Progression-Free Survival in Ovarian Cancer Patients in NOVA

	gBRCA-mutant cohort		**Non-gBRCA-mutant cohort (regardless of HRD status)**		**HRDpos (within non-gBRCA-mutant cohort)**	
	Niraparib (N=138)	**Placebo (N=65)**	**Niraparib (N=234)**	**Placebo (N=116)**	**Niraparib (N=106)**	**Placebo (N=56)**
PFS median (95% CI)	21.0 (12.9, NR)	5.5 (3.8, 7.2)	9.3 (7.2, 11.2)	3.9 (3.7, 5.5)	12.9 (8.1, 15.9)	3.8 (3.5, 5.7)
p-value	<0.0001		<0.0001		<0.0001	
Hazard ratio (Nir:Plac) (95% CI)	0.27 (0.173, 0.410)		0.45 (0.338, 0.607)		0.38 (0.243, 0.586)	

Abbreviations: CI = confidence interval; gBRCA mutant = patients with germline breast cancer gene mutation; HRD = homologous recombination deficiency; HRDpos = homologous recombination deficiency-positive; Nir = niraparib; NR = not reported; PFS = progression-free survival; Plac = placebo.
PFS is defined as the time in months from the date of first dose to progression or death
Source:[33]

The primary data to support the safety of treatment with niraparib are derived from the NOVA main study in which a total of 546 patients received study drug. All 367 patients who received niraparib and 171 (96%) of 179 patients who received placebo experienced at least 1 treatment-emergent adverse event (TEAE). The high rate of TEAEs in the placebo group indicates the burden of prior chemotherapy and the patient's underlying ovarian cancer. Review of the data across study cohorts for TEAE incidence showed that, in general, the results were similar in the g*BRCA*mut and non-g*BRCA*mut cohorts. In the overall safety population, for the niraparib vs. placebo treatment arms, the incidences of Grade 3 to 4 TEAEs (74% vs. 23%), serious adverse events (SAEs) (30% vs. 15%), TEAEs leading to treatment interruption (69% vs. 5%), TEAEs leading to dose reduction (67% vs. 15%), and TEAEs leading to treatment discontinuation (15% vs 2%) were higher for niraparib. There were no on-treatment deaths reported.

The most commonly observed nonhematologic TEAEs (all grades) observed in niraparib compared to placebo-treated patients were nausea (74% vs. 35%), fatigue (46% vs. 32%), constipation (40% vs. 20%), and vomiting (34% vs. 16%). The majority of the nonhematological TEAEs were mild to moderate in severity. The most commonly observed hematologic TEAEs (all grades) of niraparib were anemia (49%), thrombocytopenia (46%), and neutropenia (18%). Although Grade 3 to 4 hematologic laboratory events were common at the initiation of treatment, no severe clinical sequelae were observed, and relatively few patients discontinued due to these AEs. Dose adjustment based on individual tolerability during the first 3 cycles substantially

reduced the incidence of these events beyond Cycle 3, indicating the overall effectiveness of the approach to dose modification. These TEAEs can be monitored routinely using standard assessments of hematological laboratory parameters, as is routine for patients with ovarian cancer receiving anticancer therapies. In the NOVA study, niraparib dose adjustment tended to occur early with most patients reaching their individual adjusted dose level at the end of Month 3 (ie, Cycle 3) of treatment. Approximately 36% patients were kept on 300 mg and approximately 64% patients had dose adjustments after 3 cycles in NOVA. However, in the Phase 1 portion of the TOPACIO study (combination of niraparib and pembrolizumab), no patients were able to tolerate the 300 mg dose of niraparib.

Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) are potential adverse class effects associated with PARP inhibitors.[34] MDS and AML therefore represent a potential risk to patients receiving niraparib. In the Phase 3 NOVA study, the incidence of MDS/AML in patients who received niraparib (5 of 367; 1.4%) was similar to its incidence in patients who received placebo (2 of 179; 1.1%). Guidance on monitoring patients for new events of MDS/AML and the follow-up of patients with suspected MDS/AML is provided in Section 13.1.8.

Study PR-30-5011-C1 (NOVA corrected QT interval [QTc] substudy n = 26) was an open-label evaluation of the effects of niraparib on QTc measurements in patients with histologically diagnosed ovarian cancer, fallopian tube cancer, or primary peritoneal cancer. There were no reports of clinically significant abnormal electrocardiogram (ECG) changes, including QTc interval prolongation, attributed to niraparib. Administration of niraparib at the therapeutic dose did not prolong the QT interval. There was no correlation between the exposure level (ie, plasma concentration) of niraparib and QTc changes (ie, changes in QTc using Fridericia's formula).

MDS and AML have been observed in patients receiving treatment with olaparib, a PARP inhibitor; given the common mechanism of action, MDS and AML therefore represent a potential risk to patients receiving niraparib.

Details of the clinical studies conducted with niraparib can be found in the current Investigator's Brochure.

5.1.1.3. Study Rationale

This study aims to investigate the preliminary antitumor activity of niraparib assessed as the change in tumor volume observed after treatment with niraparib in the neoadjuvant treatment of localized, HER2-negative, *BRCA*mut breast cancer patients.

6. TRIAL OBJECTIVES AND PURPOSE

6.1. Primary Objective

- 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, human epidermal growth factor receptor 2 (HER2) negative, breast cancer susceptibility gene (*BRCA*) mutant breast cancer patients.

6.2. Secondary Objectives

- 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
  - 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

6.3. Exploratory Objectives

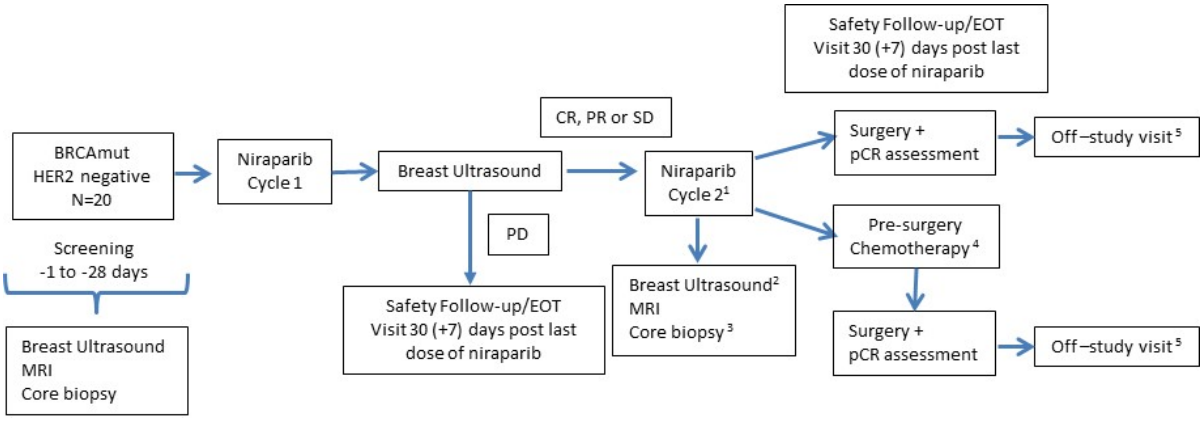
- To evaluate niraparib-induced changes in immune responses
- To explore intra-tumoral niraparib concentration and correlation with blood
- To estimate the preliminary antitumor activity of niraparib in *BRCA*mut TNBC patients and *BRCA*mut hormone-positive patients
- To evaluate pharmacodynamic inhibition of 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)

7. INVESTIGATIONAL PLAN

7.1. 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 HER2-negative and *BRCA*mut localized breast cancer (primary tumor ≥1 cm). The study design is summarized in Figure 1. If antitumor activity in the *BRCA*mut cohort is demonstrated, the protocol may be amended to add an HRD-positive, *BRCA*-wild type cohort.

Figure 1: Study Schema



[1]Patients may receive up to 6 months of niraparib (see Section 7).
[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.

Breast magnetic resonance imaging (MRI), breast ultrasound, and tumor core biopsy will be performed at the Screening (Day -28 to Day -1).

Patients will receive niraparib (200 mg orally [PO]) treatment daily for 28 days (Cycle 1) and then will undergo breast ultrasound at the end of Cycle 1 on Day 28:

- If breast ultrasound shows disease progression defined as an increase in tumor volume by greater than 20% by Investigator assessment, the patient will discontinue study. If breast ultrasound shows CR, PR or stable disease (SD) by Investigator assessment (please see Appendix 2), the patient will continue niraparib treatment 200 mg PO for an additional cycle (Cycle 2). Patients may receive up to 6 months of niraparib treatment if, in the opinion of the Investigator and Sponsor, and agreed upon by the Sponsor, the patient would benefit from additional treatment.

A breast MRI and breast ultrasound will be performed at the end of Cycle 2. The investigational team will determine if the patient will proceed to surgery or to standard of care neoadjuvant chemotherapy.

A core biopsy will be performed at the end of Cycle 2, which should occur within 24 hours of the last dose of niraparib. Niraparib treatment may be extended up to an additional 7 days after Cycle 2 Day 28 to allow for scheduling of surgery or the core biopsy:

- For those patients proceeding directly to surgery at the end of Cycle 2, a surgical biopsy may be obtained at the time of surgery provided that surgery occurs within 24 hours of the last dose of niraparib on Cycle 2 Day 28 (+7 days).
- For all other patients, provided that their tumors are amenable to biopsy, a core biopsy should be obtained within 24 hours of the last dose of niraparib on Cycle 2 Day 28 (+7 days). The biopsy should be performed after the MRI and ultrasound and prior to any subsequent anticancer therapy.

At the completion of all neoadjuvant therapy, patients will proceed to surgery and/or other local treatment as deemed appropriate by the investigator. For those patients who receive neoadjuvant therapy (niraparib alone or niraparib followed by chemotherapy), a pCR assessment will be made at the time of surgery.

Patients shall discontinue treatment in case of unacceptable toxicity or withdrawal of consent.

AEs, regardless of the source of identification (eg, physical examination, laboratory assessment, ECG, or reported by patient), will be collected and recorded in the electronic case report form (eCRF) for each patient from the day of signed informed consent form until 30 days after last dose of study treatment.

SAEs and adverse events of special interest (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).

Related SAEs (assessed as related to study drug by the Investigator) will be collected for each patient from the date of signed informed consent until study closeout.

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.

Any pregnancies that occur up to and including 180 days post treatment will be reported. Pregnancies occurring more than 180 days after last dose, with an associated SAE (considered causally related to the study drug by the Investigator) will follow the SAE reporting requirements.

7.1.1. General Study Conduct

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 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.

Following informed consent, all patients will undergo screening procedures within 28 days prior to the first dose of study drug to determine eligibility for study entry. Screening procedures include medical, surgical, cancer, and medication history; complete physical examination, including vital signs, height, and weight; Eastern Cooperative Oncology Group (ECOG) performance status; clinical laboratory assessments (complete blood count [CBC], serum chemistry, and urinalysis); pregnancy test for women of childbearing potential; and ECG.

Patients must have a baseline tumor assessment by ultrasound and MRI to determine extent of disease and confirm presence of measurable disease. Tumor volume will be calculated at baseline and after Cycle 2 via MRI and ultrasound as follows: (length × width × height × π)/6.[35] Patients will also undergo core biopsy at baseline and at the end of Cycle 2 obtained preferably within 24 hours of the last dose of niraparib, after the MRI and ultrasound, and prior to any subsequent anticancer therapy. 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. Niraparib treatment may be extended up to an additional 7 days after Cycle 2 Day 28 to allow for scheduling of surgery or the core biopsy. During treatment, patients will undergo a breast ultrasound at the end of each 28-day cycle. If the breast ultrasound shows disease progression defined as an increase in tumor volume by greater than 20% by Investigator assessment, the patient will discontinue the study. If the breast ultrasound shows CR, PR, or SD by Investigator assessment (please see Appendix 2) at the end of Cycle 1, the patient will continue niraparib treatment 200 mg PO for an additional cycle (Cycle 2). Patients may receive up to 6 months of niraparib treatment if, in the opinion of the Investigator and Sponsor, and agreed upon by the Sponsor, the patient would benefit from additional treatment.

At the completion of neoadjuvant treatment with niraparib, patients will be assessed for presurgery neoadjuvant chemotherapy, the appropriateness of which is up to the Investigator's clinical judgment. For those patients who receive neoadjuvant therapy (niraparib alone or niraparib followed by chemotherapy), a pCR assessment will be made at the time of surgery. ***Pathological complete response (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).

Safety assessments conducted throughout the study include symptom-directed physical examination, vital signs, ECOG performance status, clinical laboratory assessments (CBC, serum chemistry, and urinalysis) (Table 6).

Blood samples will be collected predose on Day 1 of Cycles 1 and 2, and at 2 and 4 hours post dose, and in conjunction with the post-treatment core biopsy to evaluate PK of niraparib.

Blood samples for the analysis of circulating tumor DNA (ctDNA) will be collected at Screening, on Cycle 1/Day 28 predose, on Cycle 2/Day 28 predose, and at presurgery assessment. *BRCA*, HER2,estrogen receptor (ER), progesterone (PR) status must be available for all patients. All patients will undergo a Safety Follow-up/EOT Visit occurring 30 days (+7 days) post treatment.

7.2. Number of Patients

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%.

7.3. Treatment Assignment

All patients in this single-arm study will receive neoadjuvant treatment with niraparib for 2 cycles and up to 6 cycles if, in the opinion of the Investigator and Sponsor, and agreed upon by the Sponsor, the patient would benefit from additional treatment.

7.4. Dose Adjustment Criteria

Dose interruption and/or reduction may be implemented at any time for any grade toxicity considered intolerable by the patient. In addition, protocol-defined criteria for dose modification are discussed below.

Treatment must be interrupted for any treatment- related non-hematologic Common Terminology Criteria for Adverse Events v 4.03 (CTCAE), Grade 3 or 4 AE or SAE that the Investigator considers to be related to the administration of niraparib. If the toxicity is resolved to baseline or Grade ≤1 within 28 days, the patient may restart treatment with niraparib but with a dose level reduction unless prophylaxis is considered feasible (Table 4). If the event recurs at a similar or worse grade, treatment should be interrupted again, and upon resolution, a further dose reduction must be made. If upon rechallenging with niraparib at the lowest allowable dose, any CTCAE Grade 3 or 4 AEs recur, the patient must be discontinued. At the Investigator's discretion, following dose interruption (no longer than 28 days), patients may be considered for a dose reduction (no more than 1 dose reduction will be permitted). For major surgery, up to 28 days of drug interruption is allowed.

In the case of dose interruptions, the next cycle will follow the patient's original calendar schedule. Cycle timing will not be delayed for treatment interruptions, and tumor assessment should occur according to this schedule regardless of whether study drug is interrupted. Additional laboratory work-up prior to next treatment initiation should also be performed at the physician's discretion. Missed doses of niraparib (ie, any dose that is not administered within the protocol-defined administration window) will not be taken at a later date.

If the toxicity requiring dose interruption has not resolved completely or has not been reduced to NCI-CTCAE v.4.03 criteria Grade ≤1 during a maximum of 4 weeks (28 days) of dose interruption period, and/or the patient has already undergone a maximum of one dose reduction (to a minimum dose of 100 mg QD), the patient must permanently discontinue treatment with niraparib.

Table 4: Niraparib Dose Reductions for Non-Hematologic Toxicities

Event	Dose[1]
Initial dose	200 mg QD
First dose reduction for treatment-related CTCAE Grade 3 or 4 AE or SAE where prophylaxis is not considered feasible	100 mg QD
Continued treatment-related CTCAE Grade 3 or 4 AE or SAE ≥28 days	Discontinue study medication

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events SAE = serious adverse event; QD = once daily
Dose not to be decreased below 100 mg daily

Management of hematologic toxicities is described in Table 5. For Grade 3 or 4 neutropenia, thrombocytopenia, or anemia, treatment with niraparib must be interrupted with weekly blood counts monitored until recovery (neutrophils ≥1,500/µL, platelets ≥100,000/µL, or hemoglobin ≥9.0 g/dL, respectively). Niraparib should be resumed with a dose level reduction at that time. Cytokines (granulocyte colony stimulating factor) may be administered as clinically indicated according to local standard of care.

For major surgery not related to the breast tumor, up to 28 days of drug interruption is allowed.

Thrombocytopenia is an expected event associated with the use of niraparib and is described in the Investigator's Brochure. Thrombocytopenia associated with the use of niraparib resolved upon treatment interruption and/or dose reduction. The occurrence of thrombocytopenia during Cycle 1 requires additional patient monitoring in order to identify hematologic changes early and prevent higher grade thrombocytopenic events. A weekly monitoring of CBC during the first month is considered mandatory.

If a patient completes the first cycle with no incidence of hematologic toxicity requiring dose interruption or modification, then CBC monitoring will proceed according to protocol every 3 weeks, thereafter. If dose interruption or modification is required at any point on study, weekly CBC will be required for another 4 weeks after the AE has been resolved, to ensure safety of the new dose, after which monitoring every 3 weeks may resume.

Any patient requiring transfusion of platelets or red blood cells (on two different occasions) or hematopoietic growth factor support must undergo a niraparib dose reduction upon recovery if study drug is resumed.

It is strongly recommended to refer the patient to the hematologist for further evaluation if (1) transfusions are required on more than 2 occasions in the absence of non-treatment related causes or (2) the treatment-related hematologic toxicities have not recovered to allow retreatment with niraparib after 4 weeks. If a diagnosis of MDS/AML is confirmed by a hematologist, the patient must permanently discontinue study drug.

Table 5: Management of Hematologic Toxicities

Platelet count <100,000/µL	First occurrence: • Withhold study medication for a maximum of 28 days and monitor blood

	counts weekly until platelet counts return to ≥100,000/µL. • Resume study medication at same or reduced dose per Table 4. • If platelet count is <75,000/µL, resume at a reduced dose.
	Second occurrence: • Withhold study medication for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥100,000/µL. • Resume study medication at a reduced dose per Table 4. • Discontinue study medication if platelet count has not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone dose reduction to 100 mg once daily.[1]
Neutrophil <1,000/µL or Hb <8 g/dL	• Withhold study medication for a maximum of 28 days and monitor blood counts weekly until neutrophil counts return to ≥1,500/µL or Hb returns to ≥9 g/dL. • Resume study medication at a reduced dose per Table 4. • Discontinue study medication if neutrophils and/or Hb has not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone dose reduction to 100 mg once daily.[1]
Hematologic adverse reaction requiring transfusion	• For patients with platelet count ≤10,000/µL, platelet transfusion should be considered. If there are other risk factors such as co-administration of anticoagulation or antiplatelet drugs, consider interrupting these drugs and/or transfusion at a higher platelet count. • Resume study medication at a reduced dose.
Confirmed myeloplastic syndrome or acute myeloid leukemia	• Permanently discontinue treatment

Abbreviations: Hb = hemoglobin.

7.5. Criteria for Study Termination

The Sponsor may terminate this study at any time. The Sponsor will notify the Investigators when the study is to be placed on hold, completed, or terminated.

7.6. Schedule of Events

The schedule of events for this study is provided in Table 6.

Table 6: 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		
Breast ultrasound tumor assessment	X					X[4]		X[4]		X[4]			
Breast MRI tumor assessment	X							X[4]					

Table 6: Schedule of Events (Continued)

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**
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												
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												

Table 6: Schedule of Events (Continued)

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**
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				
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.

8. SELECTION AND WITHDRAWAL OF PATIENTS

8.1. Patient Inclusion Criteria

To be eligible for participation in this study, patients must meet all of the following criteria:

1. Patients age ≥18 years old
2. Patients with a deleterious or suspected deleterious *BRCA1* or *BRCA2* mutation (germline or somatic) may be enrolled into the study based on either local or central laboratory testing of *BRCA* status
3. Histologically-confirmed HER2-negative localized breast cancer by core biopsy.
4. Primary operable, non-metastatic invasive carcinoma of the breast, confirmed histologically by core biopsy. Fine-needle aspiration is not sufficient. Incisional biopsy is not allowed. In patients with multifocal and/or multicentric, the largest lesion should be measured. Both unilateral and bilateral breast cancer are allowed.
5. Primary tumor size ≥1 cm
6. Measurable disease by breast ultrasound and MRI
7. ECOG performance status of 0 or 1
8. Adequate organ function, defined as follows:

Note: CBC should be obtained without transfusion or receipt of colony stimulating factors within 4 weeks prior to obtaining a sample.

   a. ANC ≥ 1,500/μL
   b. Platelets ≥ 100,000/μL
   c. Hemoglobin ≥ 9 g/dL
   d. Serum creatinine ≤ 1.5 x upper limit of normal (ULN) or calculated creatinine clearance ≥ 50 mL/min using Cockcroft-Gault equation
   e. Total bilirubin ≤ 1.5× ULN except in patients with Gilbert's syndrome. Patients with Gilbert's syndrome may enroll if direct bilirubin ≤ 1.5 × ULN of the direct bilirubin
   f. AST and ALT ≤ 2.5 x ULN

9. Patient must have recovered to Grade 1 toxicity from prior cancer therapy (a patient with Grade 2 neuropathy or Grade 2 alopecia is an exception to this criterion and may qualify for this study).
10. Able to take oral medications
11. Patient meets the following criteria:

    a. Female patient (of childbearing potential) is not breastfeeding, has a negative serum pregnancy test within 72 hours prior to taking study drug, and agrees to abstain from activities that could result in pregnancy from Screening through 180 days after the last dose of study drug, or is of nonchildbearing potential.

Note: A urine pregnancy test may be performed if the serum pregnancy test is not available before dosing.

b. Female patient is of non-childbearing potential (other than medical reasons) as defined by the following:
   i. ≥45 years of age and has not had menses for >1 year.
   ii. Amenorrheic for <2 years without a hysterectomy and oophorectomy and a follicle-stimulating hormone value in the postmenopausal range upon Screening evaluation.
   iii. Had undergone a hysterectomy, bilateral oophorectomy, or tubal ligation. Documented hysterectomy, oophorectomy, or tubal ligation must be confirmed in the medical records; otherwise the patient must be willing to use 2 adequate barrier methods throughout the study starting from the Screening visit through 180 days after the last dose of study drug. Please see Section 9.2.2 for a list of acceptable birth control methods. Information must be captured appropriately within the site's source documents.

c. Male patient agrees to use an effective method of contraception (please see Section 9.2.2 for a list of acceptable birth control methods) starting with the first dose of study therapy through 120 days after the last dose of study therapy.

   Note: Abstinence is acceptable if this is the established and preferred contraception for the patient.

12. Able to understand the study procedures and agree to participate in the study by providing written informed consent

8.2. Patient Exclusion Criteria

To be eligible for participation in this study, patients may not meet any of the following criteria:

1. Prior anti-cancer therapies for current malignancy
2. Known evidence of distant metastasis. Staging studies are not required.

   The decision to pursue staging studies is at the discretion of the treating clinician, based on the patient's clinical and pathologic findings consistent with standard guidelines.
3. Known hypersensitivity to the components of niraparib components or their formulation excipients
4. Major surgery within 3 weeks of starting the study or patient has not recovered from any effects of any major surgery
5. Poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 90 days) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, uncontrolled hypertension, active uncontrolled coagulopathy, bleeding disorder, or any psychiatric disorder that prohibits obtaining informed consent

6. History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the patient's participation for the full duration of the study drug, or is not in the best interest of the patient to participate
7. Patient is pregnant or breastfeeding, or expecting to conceive children within the projected duration of the study drug or within the 180-day period after the last dose of study drug.
8. Immunocompromised patients (Note: patients with splenectomy are allowed).
9. Known active hepatic disease (ie, Hepatitis B or C)
10. Prior treatment with a known PARP inhibitor
11. Other active malignancy that warrants systemic therapy
12. Known history of MDS or AML

8.3. Restrictions During Study

1. Patients of child bearing potential and their partners who are sexually active (exception: abstinence for the total duration of the trial), must agree to the use of two highly effective forms of contraception throughout their participation during the study treatment and for 180 days after last dose of study treatment(s):
   a. Condom with spermicide and one of the following:
      - Oral contraceptive or hormonal therapy (eg, hormone implants)
      - Placement of an intrauterine device (IUD)

   Acceptable non-hormonal birth control methods include:

   b. Total sexual abstinence for the total duration of the trial, defined as the time from the patient's signing of the main ICF through the drug washout period. The washout period for niraparib is at least 90 days
   c. Vasectomized sexual partner plus male condom with spermicide and participant assurance that partner received post-vasectomy confirmation of azoospermia
   d. Tubal occlusion plus male condom with spermicide
   e. IUD plus male condom with spermicide

   Acceptable hormonal methods include:

   f. Etonogestrel implants (eg, Implanon, Norplan) plus male condom with spermicide
   g. Normal and low dose combined oral pills plus male condom with spermicide
   h. Norelgestromin/ethinyl estradiol transdermal system plus male condom with spermicide
   i. Intravaginal device plus male condom with spermicide (eg, ethinyl estradiol and etonogestrel)
   j. Cerazette® (desogestrel) plus male condom with spermicide. Cerazette is currently the only highly efficacious progesterone-based pill

8.4. Patient Withdrawal Criteria

8.4.1. Discontinuation from Treatment

Patients may be discontinued from study drug at any time. Specific reasons for discontinuing all study drugs include the following:

- Unacceptable toxicity that cannot be managed by dose modification
- Disease progression as outlined per Response Evaluation Criteria in Solid Tumors v1.1[36]
- In the best interest of the patient as judged by the Investigator and/or Sponsor
- Severe noncompliance with the protocol as judged by the Investigator and/or Sponsor
- Withdrawal of consent
  - Note: All reasonable efforts should be made to encourage patients to remain on study even if they withdraw from treatment.
- Patient becomes pregnant
- Sponsor decision to terminate study
- Death

Details of required niraparib dose modifications, including interruptions, dose reductions, and permanent discontinuations, related to toxicity, are provided in Section 7.4 .

Patients who discontinue from study drug will continue to receive follow-up assessments (Table 6) as part of the study unless they are discontinued from the study.

8.4.2. Discontinuation from the Study

Patients may be discontinued from the study for any of the following reasons:

- Withdrawal of consent by the patient, who is at any time free to discontinue their participation in the study
- Death from any cause
- Lost to follow-up
- Sponsor decision to terminate study

Patients who withdraw from study drug will be asked to continue the study visits and assessments as outlined in the Schedule of Events (Section 7.1.1, Table 6). If a patient is lost to follow-up, attempts should be made to contact the patient to determine the reason for discontinuation. For patients who are lost to follow-up, at least three documented attempts, including one via certified mail, should be made to contact the patient before considering the patient lost to follow-up.

If a patient discontinues study drug prior to the second MRI assessment of disease (scheduled radiological assessment at the end of Cycle 2), the patient may be replaced for the purposes of

efficacy analysis after consultation between the Sponsor and Investigator. The efficacy analysis population includes all patients who completed 2 cycles of treatment.

9. TREATMENT OF PATIENTS

9.1. Description of Study Drug

Table 7: Investigational Product

	Investigational Product
Product Name:	**Niraparib**
Dosage Form:	**100 mg capsule**
Unit Dose	**2 capsules of 100 mg each (200 mg/day)** **Administered once daily**
Route of Administration	**PO**
Physical Description	**Capsules**

Abbreviation: PO = oral

9.2. Concomitant Medications

Any medication the patient takes during the study other than the study drugs, including herbal and other nontraditional remedies, is considered a concomitant medication. All concomitant medications must be recorded in the eCRF. The following information must be recorded in the eCRF for each concomitant medication: generic name, route of administration, start date, stop date, dosage, and indication. Any changes in the dosage or regimen of a concomitant medication must be recorded in the eCRF.

At screening, patients will be asked what medications they have taken during the last 30 days. At each subsequent study visit, patients will be asked what concomitant medications they are currently taking or have taken since the previous visit.

Niraparib weakly induces cytochrome P450 (CYP)1A2 in vitro and is an insensitive substrate for P-glycoprotein (P-gp); therefore, investigators should be advised to use caution with drugs that are the sensitive substrates for CYP1A2 with a narrow therapeutic range, i.e. theophylline and tizanidine.

9.2.1. Prohibited Medications

Patients are prohibited from receiving the following therapies during the screening and treatment phase of this study:

- Antineoplastic systemic chemotherapy or biological therapy
- Radiation therapy or immunotherapy
- Chemotherapy during niraparib treatment
- Investigational agents other than niraparib
- Live vaccines within 30 days prior to the first dose of study drug and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, Bacille

Calmette-Guerin, and typhoid (PO) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (eg, Flu-Mist®) are live attenuated vaccines and, therefore, are not allowed.

- Prophylactic cytokines (granulocyte colony-stimulating factor) should not be administered in the first cycle of the study but may be administered in subsequent cycles according to current American Society of Clinical Oncology guidelines.[37]

If there is a clinical indication for any medication or vaccination specifically prohibited during the study, discontinuation from study drug may be required. The Investigator should discuss any questions regarding this with the Sponsor. The final decision on any supportive therapy or vaccination rests with the Investigator and/or the patient's primary physician. The decision to continue the patient on study drug, however, requires the mutual agreement of the Investigator, the Sponsor, and the patient.

9.2.2. Contraception

Niraparib is known to have properties that require the patient to use contraception. For details on niraparib, please refer to the Investigator's Brochure.

The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide per local regulations or guidelines. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including PO, subcutaneous, intrauterine, or intramuscular agents). Abstinence is acceptable if this is the established and preferred contraception for the patient.

Patients should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study. In order to participate in the study female patients must adhere to the contraception requirement (described above) for the duration of the study and through 180 days after the last study drug. Male patients should not donate sperm or father children from screening throughout the duration of the study up to 120 days after the last dose of study drug is received. If there is any question that a patient will not reliably comply with the requirements for contraception, that patient should not be entered into the study.

9.2.3. Other Study Restrictions

Patients who are blood donors should not donate blood during the study and for 90 days after the last dose of study drug.

Patients should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting.

9.3. Treatment Compliance

Compliance with inclusion and exclusion criteria will be assessed as outlined in Section 8 and Section 8.2, respectively.

Niraparib will be administered by site personnel at study sites as detailed in Section 10.5.

Study drug accountability will be monitored as detailed in Section 10.7.

9.4. Randomization and Blinding

Not applicable; this is a single-arm, open-label study.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

Niraparib ([3S]-3-[4- phenyl] piperidine [tosylate monohydrate salt]) is a PO available, potent, highly selective PARP1 and PARP2 inhibitor. The excipients for niraparib are lactose monohydrate and magnesium stearate. Niraparib will be supplied as 100 mg capsules.

10.2. Study Drug Packaging and Labeling

Niraparib 100 mg capsules may be packed in high-density polyethylene bottles with child-resistant closures or in blister cards. The Sponsor is exploring a change in packaging configuration to blister cards, which may be implemented at some point during the study.

The label text of the study drug will comply with Good Manufacturing Practice and national legislation to meet the requirements of the participating countries. The study drug will be open-label and nonpatient-specific.

All study drug supplies must be stored in accordance with the Pharmacy Manual instructions and package labeling. Until dispensed or administered to the patients, the study drug will be stored in a securely locked area, accessible to authorized personnel only.

10.3. Study Drug Storage

All study drug supplies must be stored in accordance with the Pharmacy Manual instructions and package labeling. Until dispensed or administered to the patients, the study drug will be stored in a securely locked area, accessible to authorized personnel only.

10.4. Study Drug Preparation

The Pharmacy Manual contains descriptions of the packaging of study drug and instructions for administration of study drug.

10.5. Administration

Niraparib (100 mg niraparib capsules) will be supplied and starting dose will be 200 mg. Study drug will be administered PO daily throughout 28 days for 2 cycles, with the potential for an additional 4 cycles (maximum total of 6 cycles) at the assigned dose and schedule.

Patients will be instructed to take study drug at approximately the same time each day. Bedtime administration may be a potential method for managing nausea. Patients must swallow capsules whole. Study drug may be taken with or without food. Study drug will be dispensed to patients on Day 1 of each cycle if breast ultrasound shows CR, PR, or SD after the previous cycle of niraparib treatment (please see Appendix 2).

The Pharmacy Manual contains descriptions of the packaging of study drug and instructions for administration of study drug.

10.6. Presurgery Chemotherapy

The decision to proceed to surgery or to pursue neoadjuvant chemotherapy following treatment with niraparib will be at the discretion of the treating investigator. Details regarding neoadjuvant chemotherapy, including agents, start and stop dates, will be recorded in the eCRF.

10.7. Study Drug Accountability

The Investigator or designee is responsible for maintaining accurate dispensing records of the study treatments throughout the clinical study. Study drug accountability should be maintained by each site based on the capsules dispensed versus returned to the clinic at each visit and the number of days since the last visit.

Details of maintaining drug accountability, including information on the accountability log, will be provided in the Pharmacy Manual.

All dispensation and accountability records will be available for the Sponsor review. The Study Monitor will assume the responsibility to reconcile the study treatment accountability log. The pharmacist will dispense study treatment for each patient according to the protocol and the Pharmacy Manual, if applicable.

10.8. Study Drug Handling and Disposal

At the end of study, when all patients have stopped protocol treatment, complete drug reconciliation per batch should be available at the site for verification in order to allow drug destruction or return procedure. After receiving Sponsor approval in writing, the investigational site is responsible for destruction of study drug according to local regulations. If a site does not have the capability for onsite destruction, the Sponsor will provide a return for destruction service to a third party. Both the unused and expired study drug must be destroyed, upon authorization of the Sponsor, according to local regulations and procedures, and a copy of the destruction form must be filed in the study binder.

The medication provided for this study is to be used only as indicated in this protocol and only for the patients entered in this study.

11. ASSESSMENT OF EFFICACY

11.1. Efficacy Endpoints

11.1.1. Primary 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. Tumor volume will be calculated as (length × width × height × π)/6.[35]

11.1.2. Secondary Endpoints

- pCR: 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[1]).
- Tumor response rate based on the change in tumor volume as measured by breast ultrasound; a response is considered ≥30% reduction of tumor volume from baseline after 2 months of niraparib treatment. Tumor volume will be calculated as (length × width × height × π)/6.[35]
- 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.[35]
- 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.[35]

11.2. Exploratory 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 *BRCA*mut TNBC patients and in *BRCA*mut 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, LOH) in ctDNA or tumor tissue

- Targeted (or whole exome) sequencing for other disease related molecular alterations with remaining blood or tumor samples

12. TRANSLATIONAL RESEARCH

The overall aims of translational research are the following: to evaluate the effect of niraparib treatment on the tumor immune contexture, as well as PD changes in the tumor; to explore molecular mechanisms mediating resistance to niraparib; and to assess the potential of blood-based predictive biomarkers, such as circulating tumor DNA.

12.1. Effect of Niraparib Treatment on the Tumor Immune Contexture and Pharmacodynamic Changes in Tumor Cells

12.1.1. Tumor Immune Contexture

The immunologic underpinnings of a tumor play an important role in disease progression and response to anticancer therapies. However, the effect of PARP inhibitor treatment on the cancer immune response has not been well characterized. There is an emerging evidence suggesting that niraparib treatment may affect the tumor immune contexture, turning a cold (non-inflamed) tumor into a hot (inflamed) one. The effect may manifest as changes in immune-related gene expression profiles, cellular composition of tumor infiltrating immune cells (eg, T cells, myeloid cells, NK cells), as well as signaling pathways (eg, STING/IFN a/b), and chemokine/cytokine profiles. Better understanding of the immune modulatory effect of niraparib will help the development of more effective combination therapies. Tumor biopsies, collected in formalin-fixed paraffin embedded (FFPE) before and after niraparib treatment, will be analyzed for biomarkers related to breast cancer biology, PARP inhibition, or immune oncology (eg, gene expression profiling), as well as immune phenotyping using multiplex immunofluorescence techniques.

12.1.2. Intra-tumoral Niraparib Concentration

Efficient tumor penetration is essential for achieving complete inhibition of PARP activity in all malignant cells within a tumor nodule. Preclinical data showed that niraparib has excellent tumor penetrance property. To evaluate concentration of niraparib in tumors, a post-treatment biopsy, collected within 24 hours after last dose of niraparib is needed. Niraparib concentration in tumor will be correlated with blood PK parameters, PD endpoints, and efficacy outcomes.

12.1.3. Pharmacodynamic Changes

Niraparib is a potent and selective inhibitor of PARP1 and PARP2. In tumors with deficiency in homologous recombination, the inhibition of PARP activity will lead to accumulation of unrepaired DNA damage and cell death. Fresh frozen tumor biopsies, collected before and after niraparib treatment, will be analyzed for PARP enzymatic activity (eg, PARylation assay). In addition, the FFPE biopsies will be analyzed for DNA damage and repair (eg, γH2AX, RAD51), proliferation (eg, Ki67), and cell death (eg, Cleaved Caspase 3)-related biomarkers.

The studies detailed above will be conducted on frozen and FFPE core biopsies collected during the Screening and again at the end of Cycle 2. The biopsy at the end of Cycle 2 should be taken within 24 hours of the last dose of niraparib, whenever possible, to preserve the effects induced by niraparib treatment. 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.

12.1.4. Molecular Mechanisms Mediating Resistance to Niraparib in *BRCA*mut Population

*BRCA*mut leads to malignancies deficient in homologous recombination and responsiveness to PARP inhibitors. However, many changes within the tumor (eg, *BRCA* reversion mutation, loss of 53BP1 expression) can partially restore homologous recombination function and cause resistance to PARP inhibitors. In addition, it has been shown that, in ovarian cancer patients with germline *BRCA* mutations, loss of heterozygosity (LOH) in the tumor is correlated with stronger clinical benefit from platinum based therapies. To study these sensitivity/resistance mechanisms, tumor sample from surgery may be deep sequenced to look for coexistent genomic alternations. If enough RNA can be extracted, gene expression of these tumors may be evaluated by sequencing technology or alternative methods.

12.2. Assessment of Blood-based Predictive Biomarkers for Niraparib Efficacy and Resistance

12.2.1. *BRCA* Status and Other Biomarker Analysis of Circulating Tumor DNA

Plasma of most cancer patients contains ctDNA that carries information on tumor mutations and tumor burden. This information can be reliably retrieved with deep sequencing technology and may be useful as a minimally-invasive way of monitoring cancer genomic alterations (mutations, rearrangements). A next-generation sequencing (NGS)-based ctDNA panel, which includes both *BRCA1* and *BRCA2*, has been developed and validated for investigational use only. This test can be used to identify patients with *BRCA1/2* mutations for enrollment into this study. In addition, ctDNA analyses may allow tracking and monitoring of tumor dynamics during treatment, as well as the emergence of resistant subclones. ctDNA analysis will be conducted to evaluate genomic alternations, such as BRCA reversion mutations, LOH, and their correlation with response to treatment.

12.3. Summary of Sample Collection

The required samples for biomarker assessment are presented in Table 8.

Table 8: Summary of Sample Collection

Sample Type	Collection Timepoints	Sample Amount	Local Storage Conditions	Purpose
Core biopsy[1]	Screening, end of Cycle 2	Core biopsies: 4 to 5 cores (2 fresh frozen and 2 to 3 fixed in NBF) Surgical biopsy (if applicable): 2 pieces fresh frozen and 1 piece fixed in NBF	-80°C (fresh frozen) and room temperature (NBF fixed)	Immune contexture Tumor PK/PD
Tumor from surgery	Surgery	1 FFPE block	Room temperature	Resistance biomarkers
Blood	Screening, end of Cycle 1, end of Cycle 2, and presurgery	20 mL	-80°C or -20°C	ctDNA analysis

Abbreviations: ctDNA = circulating tumor DNA; FFPE = formalin-fixed paraffin embedded; NBF = neutral buffered formalin; PD = pharmacodynamic; PK = pharmacokinetic.
[1]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.

All samples will be collected and managed centrally when possible and will be distributed either directly or subsequently to designated translational research laboratories for biomarker testing. Details on blood and tissue sample collection, processing, storage, shipping, and handling instructions can be found in the Laboratory Manual.

12.4. Safety Endpoints

- Safety by toxicity grades as defined by the NCI-CTCAE v.4.03 criteria
- Incidence of TEAEs
- Changes in clinical laboratory parameters (hematology, chemistry)
- Vital signs
- Physical examinations
- Usage of concomitant medications

13. ASSESSMENT OF SAFETY

13.1. Safety Parameters

Safety will be evaluated based on the incidence of TEAEs, SAEs, treatment discontinuations or dose reductions due to AEs, changes in clinical laboratory results (hematology and chemistry), vital sign measurements, observations during physical examination, and use of concomitant medications. All AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA) coding system.

13.1.1. Demographic/Medical History

Demographic and baseline characteristics consist of those variables that are assessed at screening. Patient demography consists of age at screening, race, ethnicity, and sex.

13.1.2. Disease History

For disease history, the following will be documented:

- Date of first diagnosis of breast cancer
- Histology at diagnosis and most recent biopsy, if additional biopsy performed

13.1.3. Medical and Surgical History

Major medical and surgical history (including medication history), including history of thrombocytopenia, neutropenia, leukopenia, or anemia will be collected. Details of any prior invasive malignancy will be collected. Medical and surgical history will be obtained by interviewing the patient or by reviewing the patient's medical records.

13.1.4. Vital Signs

Vital signs (blood pressure, pulse, and temperature) will be assessed according to the Schedule of Events (Table 6).

Any vital signs assessed as clinically significant should be recorded as an AE or SAE. If SAE criteria are met or the abnormality is an AESI, the event should be recorded and reported according to the SAE reporting process (see Section 13.2.5).

13.1.5. Weight and Height

Body weight and height will be assessed according to the Schedule of Events (Table 6).

13.1.6. Physical Examination

Complete physical examination, symptom-directed physical examination, and physical breast examinations will be performed in accordance with the Schedule of Events (Table 6).

Any physical examination or physical breast examination assessed as clinically significant should be recorded as an AE or SAE. If SAE criteria are met or the abnormality is an AESI, the event should be recorded and reported according to the SAE reporting process (see Section 13.2.5).

13.1.7. Electrocardiogram

All patients will undergo ECGs in accordance with the Schedule of Events (Table 6). ECGs should be performed prior to blood draws. Patients will be supine and rested for approximately 2 minutes before ECGs are recorded.

Any ECG findings assessed as clinically significant should be recorded as an AE. If SAE criteria are met or the abnormality is an AESI, the event should be recorded and reported according to the SAE reporting process (see Section 13.2.5).

13.1.8. Clinical Laboratory Assessments

The hematology, blood chemistry, urinalysis, and pregnancy screening will occur in accordance with the Schedule of Events (Table 6). These tests will be performed by the local laboratory at the clinical site. For any patient diagnosed with MDS/AML while on study, a bone marrow aspirate and biopsy and sample collection (whole blood) for cytogenetic analysis will be obtained.

13.1.8.1. Hematology

Hematology will be measured in accordance with the Schedule of Events (Table 6). The following values will be obtained/analyzed:

- **CBC:**
  - Hemoglobin
  - Platelet count
  - Mean corpuscular volume
  - White blood cell count
  - Differential white blood cell count

13.1.8.2. Blood Chemistry

Blood chemistry will be assessed in accordance with the Schedule of Events (Table 6). The following values will be obtained/analyzed:

Sodium	Total bilirubin
Potassium	Alkaline phosphatase
Chloride	Aspartate aminotransferase
Creatinine	Alanine aminotransferase
Blood urea nitrogen	Total protein
Glucose	Albumin
Calcium	Amylase
Phosphate	Lactate dehydrogenase
Magnesium	

13.1.8.3. Urinalysis

Urinalysis will be assessed in accordance with the Schedule of Events (Table 6). The following values will be obtained/analyzed:

Specific gravity	Protein
Leukocyte esterase	Glucose
Nitrite	Ketones
Blood	Bilirubin

13.1.8.4. Virus Serology

Not applicable.

13.1.8.5. Drug Screen

Not applicable.

13.1.8.6. Pregnancy Screen

A negative serum pregnancy test is required within 72 hours prior to Day 1 of Cycle 1 for females of childbearing potential. If the serum pregnancy result is not available before dosing, a urine pregnancy test may be performed. Additional urine pregnancy testing will be performed in accordance with the Schedule of Events (Table 6).

13.1.9. ECOG Performance Status

Performance status will be assessed using the ECOG scale (see Appendix 1) in accordance with the Schedule of Events (Table 6). The same observer should assess performance status each time.

13.2. Adverse Events and Special Situations

13.2.1. Definition

13.2.1.1. Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of study treatment, whether or not considered related to the study treatment.

AEs may include the onset of new illness and the exacerbation of pre-existing medical conditions. An AE can include an undesirable medical condition occurring at any time after the time of randomization and/or treatment assignment, including baseline or washout periods, even if no study treatment has been administered. (See Section 13.2.3 for information about AE collecting and reporting.)

13.2.1.2. Serious Adverse Event (SAE)

Any untoward medical occurrence that, at any dose;

- Results in death;
- Is life threatening (i.e., an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe);
- Requires inpatient hospitalization* or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect; or
- Is an important medical event**

*Exception: Preplanned (at time of informed consent) hospitalization for elective procedures, for protocol compliance or social reasons, or for observation will not be considered criteria for an SAE. The reason for the planned hospitalization should be captured in medical history section in the eCRF. Complications experienced during these hospitalizations must be reported as AEs (or SAEs, if hospitalization is prolonged due to the AE).

**Medical and scientific judgment should be exercised in determining whether situations or events should be considered serious adverse events: an important medical event may not be immediately life-threatening or result in death or require hospitalization but may jeopardize the patient or require intervention to prevent one of the above outcomes. Examples of such events are allergic bronchospasm, blood dyscrasias, or convulsions that may require intensive treatment in an emergency room or at home but do not result in hospitalization, development of drug dependency or drug abuse, and transmission of disease associated with the administration of the study drug. (See Section 13.2.5 for information about SAE reporting.)

13.2.1.3. Treatment-Emergent Adverse Event (TEAE)

Any event that was not present prior to the initiation of study treatment or any event already present that worsens in either intensity or frequency following exposure to study treatment.

13.2.1.4. Adverse Event of Special Interest (AESI)

Any AE (serious or non-serious) that is of scientific and medical concern specific to the study treatment, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is appropriate.

13.2.1.5. Special Situations: Abuse, Misuse, Medication Errors, Overdose, and Accidental or Occupational Exposure

- **Abuse:** is the persistent or sporadic, intentional excessive use of the study treatment which is accompanied by harmful physical or psychological effects.
- **Misuse:** medicinal product is intentionally and inappropriately used not in accordance with the authorized/approved product information.

- **Medication error:** is any preventable incident that may cause or lead to inappropriate study treatment use or patient harm while the study treatment is in the control of the health care professionals or patients. Such incident may be due to health care professional practice, product labeling, packaging and preparation, procedures for administration, and systems, including the following: prescribing, order communication, nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use.
- **Overdose:** is a deliberate or accidental administration of study treatment to a study patient, at a dose greater than that which was assigned to that patient per the study protocol and under the direction of the Investigator. If an overdose occurs, the Investigator and the Sponsor should be notified immediately, and the patient should be observed closely for AEs. Associated AEs should be treated and monitored by the Investigator. The dosage of study drug administered, any associated AEs, and/or treatment provided to the patient because of the overdose, should be documented on the applicable sections within the eCRF. An overdose (including an AE or SAE resulting from the overdose, if any) will be reported as described in Section 13.2.5.
- **Accidental /Occupational exposure:** is the unintentional exposure to a study treatment as a result of one's professional or non-professional occupation, or accidental exposure to a non-professional to whom exposure was not intended (i.e., study product given to wrong patient).

Reporting Special Situations: All occurrences of abuse, misuse, medication error, overdose, and accidental or occupational exposure with any study treatment must be reported on an SAE Report Form [or designated Special Form] to the Sponsor regardless of whether or not an AE or SAE has occurred. If the abuse, misuse, medication error, overdose, or accidental / occupational exposure is associated with an SAE, an SAE report form must be submitted to the Sponsor within 24 hours of awareness. If there is no AE or SAE, the occurrence must be submitted on the designated Special Form (indicate 'no AE has occurred') as soon as possible.

13.2.2. Assessment of Adverse Events

13.2.2.1. Severity Assessment

All AEs will be assessed by the Investigator for severity* according to Common Terminology Criteria for Adverse Events (CTCAE) v4.03: 14 June 2010; National Institutes of Health (NIH), National Cancer Institute (NCI). The CTCAE severity grades 1 through 5 provide unique clinical descriptions of severity of each adverse event. The CTCAE v4.03 is available on the NCI/NIH website.

Please note that there is a distinction between **serious** and **severe** AEs: Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 13.2.1.2. For example, a mild degree of gastrointestinal bleeding requiring an overnight hospitalization for monitoring purposes may be considered an SAE but is not necessarily severe.

13.2.2.2. Relationship to Study Intervention

The Investigator must provide a causality assessment regarding the relationship of the event with the study drug and/or study procedure for all AEs. One of the following categories should be selected based on medical judgment, considering all contributing factors:

- Related: A causal relationship between the medicinal product (and/or study procedures) and AE is a reasonable possibility. For example, the occurrence of the AE cannot be explained by other causative factors. The AE, however, can be explained by pharmacological effect of the medicinal product such as a similar event having been reported previously, alteration of the dose effect, or the timing or seriousness of the AE, etc. Positive rechallenge/dechallenge is supportive.
- Not Related: A causal relationship between the medicinal product (and/or study procedures) and AE is not a reasonable possibility: there is no temporal relationship between the medicinal product and event, or an alternative etiology is more reasonable.

13.2.2.3. Expectedness

The Sponsor will be responsible for determining whether an adverse event is 'expected' or 'unexpected'. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information provided in the Reference Safety Information of the effective niraparib Investigator Brochure (IB).

13.2.3. Collection and Recording Adverse Events

AEs may be volunteered spontaneously by the study patient, or discovered by the study staff during physical examinations or by asking an open, nonleading question such as, "How have you been feeling since your last study visit?" The Investigator will document the nature of AE, date of onset of the AE (and time, if known), date of outcome of the AE (and time, if known), severity of the AE, action taken with study drug as a result of the AE, assessment of the seriousness of the AE, and assessment of the causal relationship of the AE to study drug and/or study procedure.

AEs, including laboratory abnormalities that are assessed as clinically significant or require intervention, should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be recorded as a separate AE.

All SAEs will be collected from the signing of the ICF for this study through 90 days after the last dose of study drug (or to a minimum of 30 days post treatment if the patient starts alternate anticancer therapy and recorded in the eCRF. SAEs will also be reported on an SAE form as described in Section 13.2.5 of this protocol. SAEs considered by the Investigator to be related to study medication are reported until study closeout.

All AEs, regardless of the source of identification (e.g., physical examination, laboratory assessment, ECG, or reported by patient), will be collected and recorded in the eCRF for each patient from the signing of the ICF for this study until 30 days after last study drug administration.

Concomitant illnesses that existed before entry into the study will not be considered AEs unless the illness worsens during the Treatment Period. Pre-existing conditions will be recorded as Medical History in the eCRF and on the SAE Report Form.

Disease progression is an efficacy criterion and is therefore not considered an AE or SAE (even if fatal). Disease progression should be reported within the eCRF. If AEs/SAEs occur in relation to disease progression that are not consistent with the natural progression of the patient's disease, these AEs/SAEs must be reported per AE/SAE reporting requirements described in Section 13.2.5.

13.2.4. Follow-Up of Adverse Events

All AEs experienced by a patient, regardless of the suspected causality, will be monitored until the AE or SAE has resolved, until any abnormal laboratory values have returned to baseline or normal levels, until stabilized with a satisfactory explanation for the changes observed, until the patient is lost to follow-up, or until the patient has died.

If an Investigator becomes aware of an SAE after the specified follow-up period and considers the SAE related to the study drug, the Investigator should report the SAE to the Sponsor according to timelines for reporting SAEs described in Section 13.2.5.

13.2.5. Reporting

The Investigator must report all SAEs, and all follow up information to the Sponsor on an SAE Report Form within 24 hours of becoming aware of the initial event or follow-up information. The Investigator must provide a causality assessment and must sign and date all SAE Report Forms.

It is the responsibility of the Investigator to review source documentation and describe pertinent information on the SAE Report Form. If supporting documentation is requested (e.g., hospital reports, consultant reports, death certificates, autopsy reports, etc.), the Investigator should highlight all relevant and pertinent information within such documents, ensure that any patient's personal identifiers (including Medical Record number) are removed, and submit the documents with the SAE Form to the Sponsor. The Sponsor (or designee) will return a confirmation of receipt for all email reports (if received from other than a "no reply" domain) within 1 business day.

After receipt of the initial report, the Sponsor (or designee) will review the information and, if necessary, contact the Investigator to obtain further information. The Investigator must promptly respond to queries from the Sponsor.

13.2.6. Submission and Distribution of Serious Adverse Event Reports

Per regulatory requirements, if an event is assessed by the Sponsor as a Serious Unexpected Adverse Reaction (SUSAR), it is the responsibility of the Sponsor to submit the SUSAR Regulatory Authorities according to applicable regulations.

In addition, the SUSAR will be distributed to the Investigators/sites, utilizing a Council for International Organizations of Medical Sciences (CIOMS) report form, or the MedWatch 3500A form). The Investigator/site will submit a copy of the report to their respective Institutional

Review Board (IRB) or Independent Ethics Committee (IEC) per the governing institutional requirements and in compliance with local laws and guidelines.

13.2.7. Adverse Events of Special Interest

Adverse Events of Special Interest (AESI) for niraparib are the following:

- Myelodysplastic Syndromes (MDS) and Acute Myeloid Leukemia (AML)
- Secondary cancers (new malignancies [other than MDS or AML])
- Pneumonitis
- Embyro-fetal toxicity

AESI should be collected and reported as follows:

- MDS and AML along with other secondary cancers should be reported to the Sponsor through 90 days after the last dose of study drug.
- Pneumonitis should be reported to the Sponsor through 90 days after the last dose of study drug (or until the start of alternate anticancer therapy, whichever occurs first).
- Embryo-fetal toxicity should be reported as outlined in Section 13.2.8

13.2.8. Pregnancy

Pregnancies occurring while female patients are enrolled in a study, or experienced by a female partner of a male patient enrolled in a study, must be reported to the Investigator and followed to outcome. Furthermore, all pregnancies must be reported to the Sponsor. The Sponsor has the responsibility to monitor the outcome of all pregnancies reported during the clinical study.

Each pregnancy must be reported by the Investigator to the Sponsor on an Initial Pregnancy Report Form within 24 hours of becoming aware of the pregnancy. Pregnancy is not an AE, and therefore does not need to be reported as an AE in the eCRF unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication. The Investigator must follow-up all pregnancies, document the course and the outcome, and report this information to the Sponsor on a Pregnancy Outcome Report Form within 24 hours of becoming aware - even if the patient was withdrawn from the study or the study has finished.

An elective abortion without complications should not be regarded as an AE, however, it should be reported as the outcome to the pregnancy on the Pregnancy Outcome Report Form. Therapeutic abortions should be reported as a treatment procedure; the reason for the therapeutic abortion should be reported on the Pregnancy Outcome Report Form and as an AE in the eCRF. Hospitalization for normal delivery of a healthy newborn should not be considered an SAE.

Any SAE that occurs during pregnancy must be recorded on the Pregnancy Outcome Report Form, reported as an SAE on the SAE Report Form (e.g., maternal serious complications, therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, birth defect) and reported to the Sponsor within 24 hours. Hospitalization for normal delivery of a healthy newborn should not be considered an SAE.

13.2.9. Special Situations

All occurrences of abuse, misuse, medication error, overdose, and accidental or occupational exposure with any study treatment must be reported on a Special Situations Report Form to the Sponsor within 5 calendar days of becoming aware of the occurrence, regardless of whether it is categorized as an AE. If the occurrence is associated with an SAE, an SAE Report Form, along with the Special Situations Report Form, must be submitted to the Sponsor within 24 hours of awareness.

14. STATISTICS

Details of the statistical analyses presented below will be provided in the Statistical Analysis Plan (SAP). A change to the data analysis methods described in the protocol will require a protocol amendment only if it alters a principal feature of the protocol. The SAP will be finalized prior to database lock. Any changes to the methods described in the plan will be described and justified in the final clinical study report.

No formal statistical testing will be done for this study. Data will be summarized in a descriptive nature. Categorical variables will be summarized by frequency distributions (number and percentage of patients). Continuous variables will be summarized by the mean, standard deviation, median, minimum, maximum, first quartile and third quartile. Further details will be provided in the SAP.

14.1. Sample size determination

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.

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

14.2. Populations for Analysis

The **Safety population** includes all patients who received any dose of study medication. The safety population will be the primary analysis population for the safety analyses.

The **Efficacy Evaluable population** includes all patients who completed 2 cycles of treatment. The efficacy evaluable population will be the primary analysis population for the efficacy analyses.

14.3. Demographics, Medical History, Baseline Characteristics, and Concomitant Medications

Demographics, baseline characteristics, and medical history information will be summarized for the Safety population using descriptive statistics. No formal statistical comparisons will be performed.

Demographics, baseline characteristics, concomitant medications, and medical history data for each patient will be provided in data listings.

14.4. Efficacy Analyses

No formal statistical testing will be done for efficacy endpoints. Tumor response rate will be tabulated together with its 95% binomial exact CI. The change in tumor volume from baseline will be summarized using descriptive statistics. Data from patients who received neoadjuvant niraparib only will be analyzed separately from those who received neoadjuvant niraparib followed by neoadjuvant chemotherapy.

14.5. Safety Analyses

All analysis for safety endpoints is will be done in a descriptive manner. Summary statistics will be provided for safety endpoints including: TEAEs, other adverse events, AESIs, clinical laboratory evaluations (hematology, chemistry, urinalysis), vital signs, ECGs, physical examination, and use of concomitant medications.

Medical history and AEs will be coded using the most up-to-date version of MedDRA. CTCAE v4.03 will be used to grade the severity of AEs and laboratory abnormalities. Prior/concomitant medication and anticancer treatment will be coded using the World Health Organization Anatomical Therapeutic Chemical classification system.

AEs will include the following categories:

- TEAEs
  - Drug-related TEAEs
  - Grade 3, 4, and 5 TEAEs (presented by grade and overall)
  - Grade 3,4, and 5 drug-related TEAES (presented by grade and overall)
  - TEAEs resulting in study drug discontinuation
  - Most commonly reported TEAEs (ie, those events reported by ≥10% of all patients)
  - Treatment-emergent SAEs
- AESIs

Details for the safety analysis will be specified in the Statistical Analysis Plan.

15. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

15.1. Study Monitoring

Before an investigational site can enter a patient into the study, a representative of TESARO will visit the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of TESARO or its representatives. This will be documented in a Clinical Study Agreement between TESARO and the Investigator.

During the study, a monitor from TESARO or representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case report forms, and that investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms with the patient's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each patient (e.g., clinic charts).
- Record and report any protocol deviations not previously sent to TESARO
- Confirm AEs and SAEs have been properly documented on CRFs and confirm any SAEs have been forwarded to TESARO and those SAEs that met criteria for reporting have been forwarded to the IRB.

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

15.2. Audits and Inspections

Authorized representatives of TESARO, a regulatory authority, an Independent Ethics Committee or an Institutional Review Board may visit the site to perform audits or inspections, including source data verification. The purpose of a TESARO audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP) guidelines of the International Conference on Harmonization, and any applicable regulatory requirements. The Investigator should contact TESARO immediately if contacted by a regulatory agency about an inspection.

15.3. Institutional Review Board

The PI must obtain IRB approval for the investigation. Initial IRB approval, and all materials approved by the IRB for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

16. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with GCP and all applicable regulatory requirements, TESARO may conduct a quality assurance audit. Please see Section 15.2 for more details regarding the audit process.

17. ETHICS

17.1. Ethics Review

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The Investigator must submit written approval to TESARO before he or she can enroll any patient/patient into the study.

The PI is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit patients for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The PI is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. TESARO will provide this information to the PI.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

17.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Council for Harmonization/Good Clinical Practice, applicable regulatory requirements and the TESARO's policy on Bioethics.

17.3. Written Informed Consent

The PI(s) at each center will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's signed and dated informed consent must be obtained before conducting any study procedures.

The PI(s) must maintain the original, signed Informed Consent Form. A copy of the signed Informed Consent Form must be given to the patient.

18. DATA HANDLING AND RECORDKEEPING

18.1. Inspection of Records

TESARO will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, patient charts and study source documents, and other records relative to study conduct.

18.2. Retention of Records

The PI must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved 2 years following the discontinuance of the test article for investigation. If it becomes necessary for TESARO or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

19. PUBLICATION POLICY

Information regarding publication of study results is contained in the Clinical Trial Agreement for this study.

20. LIST OF REFERENCES

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21. APPENDICES

APPENDIX 1. EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

Description	Grade
CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.	

Source: [38]

APPENDIX 2. DISEASE ASSESSMENT CRITERIA

Definition of response

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% 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 greater than 20%.

APPENDIX 3. TNM DEFINITIONS

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 4. 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

APPENDIX 5. NATIONAL CANCER INSTITUTE COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

Refer to NCI CTCAE v.4.03 in the Study Reference Manual, or online at the following NCI website: http://ctep.cancer.gov/reporting/ctc.html

1. Toxicity grade should reflect the most severe degree occurring during the evaluated period, not an average.
2. When two criteria are available for similar toxicities, the one resulting in the more severe grade should be used.
3. The evaluator must attempt to discriminate between disease/treatment and related signs/symptoms.

An accurate baseline prior to therapy is essential.