Poster OT3-03-01

Open-label, single-arm study evaluating the antitumor activity and safety of niraparib as neoadjuvant treatment in patients with localized, *HER2*-negative, *BRCA*-mutant breast cancer

Hyo Han,[1] Leif W. Ellisen,[2] Erika Hamilton,[3] Hanna Irie,[4] Steven Isakoff,[2] Danijela Jelovac,[5] Andre Liem,[6] Minetta C. Liu,[7] Adriana Milillo Naraine,[8] Julie Nangia,[9] David Page,[10] James Reeves,[11] Cesar A. Santa-Maria,[5] Meghan Duncan,[12] Julie R. Graham,[12] Jian Chen,[12] Bruce J. Dezube,[12] Laura Spring[2]

[1]Moffitt Cancer Center-McKinley Outpatient Clinic, Tampa, Florida, United States; [2]Massachusetts General Hospital, Boston, Massachusetts, United States; [3]Tennessee Oncology, Nashville, Tennessee, United States; [4]Icahn School of Medicine at Mount Sinai, New York, New York, United States; [5]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, Maryland, United States; [6]Pacific Shores Medical Group, Long Beach, California, United States; [7]Mayo Clinic Rochester, Rochester, Minnesota, United States; [8]Memorial Health Care System, Hollywood, Florida, United States; [9]Baylor College of Medicine, Houston, Texas, United States; [10]Providence Portland Medical Center, Portland, Oregon, United States; [11]Florida Cancer Specialists-South, Fort Myers, Florida, United States; [12]TESARO, Inc., Waltham, Massachusetts, United States

BACKGROUND

PARP Inhibitors

- *BRCA1/2*-mutant cells are hypersensitive to inactivation of the nuclear DNA repair proteins, poly(ADP-ribose) polymerases (PARP).[1]
- The PARP inhibitors (PARPi) olaparib and talazoparib have been approved for patients with previously treated, germline *BRCA*-mutant (*BRCA*mut), *HER2*-negative breast cancer.[2,3]

Neoadjuvant Therapy

- Neoadjuvant therapy is administered to patients with operable cancers to downstage tumors to allow for less extensive surgery and to provide information about drug efficacy and risk of disease recurrence.
- A meta-analysis of 5500 women enrolled in 14 studies showed that neoadjuvant chemotherapy reduced the mastectomy rate without affecting survival outcomes.[4]
  - A pathologic complete response (pCR) following neoadjuvant chemotherapy was associated with improvements in overall survival and disease-free survival.
- A pilot study of neoadjuvant therapy with the PARPi talazoparib demonstrated promising efficacy in breast cancer patients with germline *BRCA*mut (N=13).[5]
  - The median decrease in tumor volume was 88% (range 30-98%).

Niraparib

- Niraparib is the first PARPi approved in the United States and Europe for maintenance treatment of patients with recurrent ovarian cancer regardless of *BRCA*mut status.[6]
- In preclinical models, niraparib has shown strong antitumor activity against *BRCA1*-mutant breast cancers.[7]
- Niraparib in combination with pembrolizumab has shown promising antitumor efficacy of patients with advanced or metastatic triple-negative breast cancer (TNBC).[8]

OBJECTIVES

The purpose of this trial is to assess the antitumor activity and safety of niraparib as neoadjuvant treatment in patients with localized, *HER2*-negative, *BRCA*mut breast cancer.

Primary Objective

- Evaluate preliminary antitumor activity of niraparib assessed as the tumor response rate based on change in tumor volume measured by breast MRI

Secondary Objectives

- Evaluate preliminary antitumor activity of niraparib assessed by
  - Presence of pCR defined as ypT0/Tis ypN0
  - 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
- Safety and tolerability

Exploratory Objectives

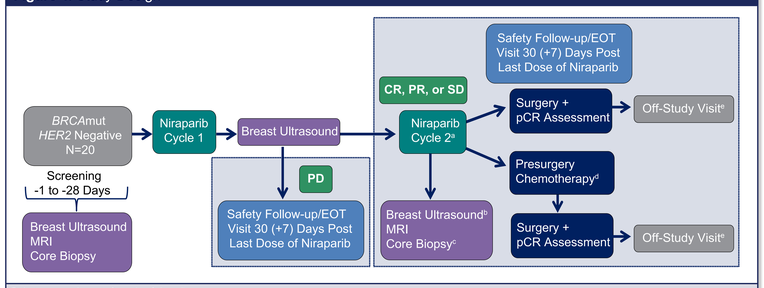
- Evaluate niraparib-induced changes in immune responses
- Explore intra-tumoral niraparib concentration and correlation with blood concentration
- Estimate the preliminary antitumor activity of niraparib in patients with *BRCA*mut TNBC and *BRCA*mut hormone-positive breast cancer
- Evaluate pharmacodynamic inhibition of PARP activity in the tumor
- Explore molecular biomarkers related to disease biology or response to treatment

METHODS

Study Design

- Open-label, single-arm pilot study enrolling patients (N≈20) with *HER2*-negative, *BRCA*mut localized breast cancer
- Patients will receive 200 mg oral niraparib once daily for 2 cycles (**Figure 1**).
  - The treating physician has the option to extend niraparib treatment to a maximum of 6 cycles.
- Breast MRI and ultrasound will be performed at the end of cycle 2 of niraparib, and the treating physician will choose if the patient will proceed to surgery, additional cycles of niraparib, or standard-of-care neoadjuvant therapy.

Figure 1. Study Design



[a]Patients may receive up to 6 months of niraparib.
[b]Breast ultrasounds are performed at the end of each month for those patients receiving additional cycles.
[c]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.
[d]Tumor size cut-off for presurgery chemotherapy will be determined by investigator discretion.
[e]Off-study visit is for the collection of pCR results for patients for whom the safety follow-up/end-of-treatment visit occurred prior to surgery; for all other patients the safety follow-up/end-of-treatment visit will act as the off-study visit.
CR, complete response; EOT, end-of-treatment; pCR, pathologic complete response; PD, progressive disease; PR, partial response; SD, stable disease.

KEY ELIGIBILITY CRITERIA

Inclusion Criteria

- Patients aged ≥18 years old
- Primary operable, nonmetastatic, *HER2*-negative, localized invasive carcinoma of the breast
  - Unilateral and bilateral cancer allowed
- Deleterious or suspected deleterious *BRCA1* or *BRCA2* mutation (germline or somatic) based on either local or central laboratory testing
- Primary tumor size ≥1 cm

Exclusion Criteria

- Prior anticancer therapies for current malignancy
- Known evidence of distant metastasis
- Prior treatment with a known PARPi

STUDY ASSESSMENTS

Efficacy

Primary Endpoint

- Tumor response rate based on the change in tumor volume as measured by breast MRI (calculated as [length x width x height x π]/6).
- A response is considered ≥30% reduction of tumor volume from baseline after 2 months of treatment.
  - Complete response: complete disappearance of all tumor signs in the breast as assessed by imaging
  - Partial response: reduction in tumor volume by ≥30%
  - Stable disease: no significant change in tumor volume (<30% reduction or <20% increase in tumor volume)
  - Progressive disease: development of new lesions or ≥20% increase in tumor volume

Secondary Endpoints

- pCR, 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 (ypT0/Tis ypN0)
- Tumor response rate based on change in tumor volume as measured by breast ultrasound. A response is considered a ≥30% reduction in tumor volume from baseline after 2 months of treatment.
- Percentage change in tumor volume from baseline after 2 months of niraparib treatment by
  - Ultrasound
  - Breast MRI

Exploratory Endpoints

- Immune-related changes in gene expression profiles and cellular composition (including T cells, myeloid cells, and natural killer cells) in tumor samples pre- and post-niraparib treatment
- Niraparib concentration in post-treatment tumor samples and correlation with pharmacokinetics in peripheral blood
- Change in tumor volume in patients with TNBC vs patients with hormone-positive tumors
- Comparison of PARP enzymatic activity, DNA damage and repair, proliferation, and survival in tumor samples pre- vs post-niraparib treatment
- Potential biomarkers of sensitivity or resistance
- Targeted (or whole exome) sequencing for other disease-related molecular alterations with remaining blood or tumor samples

Safety

- Safety will be evaluated based on adverse events, clinical laboratory analyses, vital signs, physical examinations, electrocardiograms, and concomitant medication use.

Statistical Analysis

- No formal statistical testing will be done for this study.
- Target sample size is based on clinical considerations only.

CURRENT STATUS

- This study (ClinicalTrials.gov, NCT03329937) is currently enrolling patients.
- Study is being conducted at 11 institutions (**Table 1**).
- Contact clinicaltrials@tesarobio for questions.

Table 1. Study Sites and Investigators

Site	Location	Investigator
Baylor College of Medicine	Houston, TX	Julie Nangia
Moffitt Cancer Center	Tampa, FL	Hyo Han
Tennessee Oncology	Nashville, TN	Erika Hamilton
Icahn School of Medicine at Mt. Sinai	New York, NY	Hanna Irie
Massachusetts General Hospital	Boston, MA	Steven Isakoff Laura Spring Leif Ellisen
Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins	Baltimore, MD	Cesar Santa-Maria
Pacific Shores Medical Group	Long Beach, CA	Andre Liem
Mayo Clinic Rochester	Rochester, MN	Minetta Liu
Memorial Health Care System	Hollywood, FL	Adrianna Milillo
Providence Portland Medical Center	Portland, OR	David Page
Florida Cancer Specialists-South	Fort Myers, FL	James Reeves

REFERENCES

1. Helleday T. *Mol Oncol.* 2011;5:387-93.
2. Litton JK, et al. *J Clin Oncol.* 2018;379:753-763.
3. Robson M, et al. *N Engl J Med.* 2017;377:523-533.
4. van der Hage JH, et al. *Cochrane Database of Systematic Reviews.* 2007;CD005002.
5. Litton JK, et al. *NPJ Breast Cancer.* 2017;3:49.
6. Mirza MR, et al. *N Engl J Med.* 2016;375:2154-2164.
7. Jones P, et al. *J Med Chem.* 2015;58:3302-14.
8. Vinayak S, et al. *J Clin Oncol.* 2018;36:1011-1011.

ACKNOWLEDGEMENTS

Writing and editorial support, funded by TESARO, Inc. (Waltham, MA, USA) and coordinated by Teodor G. Paunescu, PhD, and Heather Ostendorff-Bach, PhD, was provided by Jeremy Kennard, PhD, and Dena McWain of Ashfield Healthcare Communications (Middletown, CT, USA).

This presentation is the intellectual property of the author/presenter.
Contact them at publicationsteam@tesarobio.com for permission to reprint and/or distribute.