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Pilot Neoadjuvant Study of Niraparib in HER2-Negative, *BRCA*-Mutated Resectable Breast Cancer

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Background

- Niraparib is a selective oral poly(ADP-ribose) polymerase inhibitor approved in the United States and Europe as maintenance treatment for patients with recurrent ovarian cancer (OC) who are in complete or partial response to platinum-based chemotherapy and in the United States for the treatment of adult patients with advanced OC who have been treated with three or more prior chemotherapy regimens and whose cancer is associated with homologous recombination deficiency (HRD)-positive status[1,2]
- Niraparib has shown antitumor activity in advanced triple-negative breast cancer in combination with a programmed cell death 1 inhibitor[3]
  - The greatest response rate was seen in tumors with *BRCA* mutations (47%)
- Previous studies in animal and human tumors have demonstrated higher concentrations of niraparib in tumors than in plasma[4,5]
- Higher niraparib tumor concentrations were associated with improved suppression of tumor growth[4]
- A previous report from this trial showed niraparib accumulation was 36-fold higher in tumor tissue than in plasma after 2 months of treatment[6]

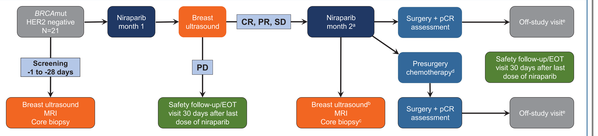
Objective

- To evaluate the antitumor activity of single-agent niraparib in the neoadjuvant treatment of patients with localized, human epidermal growth factor receptor 2 (HER2)-negative, *BRCA*-mutated breast cancer
  - The primary endpoint was tumor response rate, defined as a ≥30% reduction in tumor volume from baseline, as measured by magnetic resonance imaging (MRI) after 2 months of treatment
  - Secondary endpoints included tumor response rate, as measured by monthly ultrasound; quantified percentage change in tumor volume, as measured by MRI or ultrasound; and safety and tolerability measured for the duration of treatment

Methods

- Eligible patients were aged ≥18 years, with HER2-negative, *BRCA*-mutated (germline or somatic) resectable breast cancer with a tumor size of ≥1 cm who had not received prior treatment for the current malignancy (NCT03329937)
- Patients received oral niraparib 200 mg once daily for at least 2 months (**Figure 1**)
- At the end of 2 months, at their treating physician's discretion, patients proceeded directly to surgery, received additional cycles of niraparib (maximum of 6 months), or received neoadjuvant chemotherapy
- Additionally, niraparib concentrations were measured in tumor and plasma samples using qualified liquid chromatography–tandem mass spectrometry
  - Tumor biopsies and plasma samples were obtained at the end of the second treatment cycle

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 month 2 and before any subsequent anticancer therapy or procedure. A surgical biopsy may be used instead of a core biopsy provided that surgery occurs within 24 hours of the last dose of niraparib in month 2. [d]Tumor size cutoff 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 before 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; MRI=magnetic resonance imaging; pCR=pathologic complete response; PD=progressive disease; PR=partial response; SD=stable disease.

Results

Efficacy

- As of November 2019, 21 patients were enrolled; 21 had both an MRI and an ultrasound scan at the end of month 2 and were evaluable for response
- Demographics and baseline characteristics are shown in **Table 1**

Table 1. Patient Demographics and Baseline Characteristics

Characteristics	Total (N=21)
Age, years	
Median	43
Min, max	21, 73
Sex, n (%)	
Female	21 (100)
Race, n (%)	
White	19 (90)
Black	1 (5)
Asian	1 (5)
ECOG performance status score, n (%)	
0	20 (95)
1	1 (5)
Clinical stage, n (%)	
Stage I	8 (38)
Stage II	10 (48)
Stage III	3 (14)
Histology, n (%)	
Invasive ductal carcinoma	20 (95)
Invasive lobular carcinoma	1 (5)
***BRCA* mutation status, n (%)**	
BRCA1	14 (67)
BRCA2	6 (29)
BRCA1 and *BRCA2*, n (%)	1 (5)
Hormone receptor status, n (%)	
TNBC	15 (71)
ER- and/or PR-positive disease	6 (29)

ECOG=Eastern Cooperative Oncology Group; ER=estrogen receptor; PR=progesterone receptor; TNBC=triple-negative breast cancer.

- Six patients received post-niraparib neoadjuvant chemotherapy (NACT) (**Table 2**)

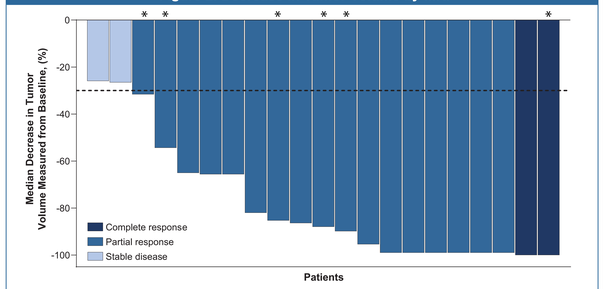
Table 2. Number of Cycles of Niraparib and Post-Niraparib NACT

Number of cycles of niraparib	Number of patients who received post-niraparib NACT
2 (n=4)	0
3 (n=8)	4
4 (n=2)	1
5 (n=2)	1
6 (n=5)	0

NACT=neoadjuvant chemotherapy.

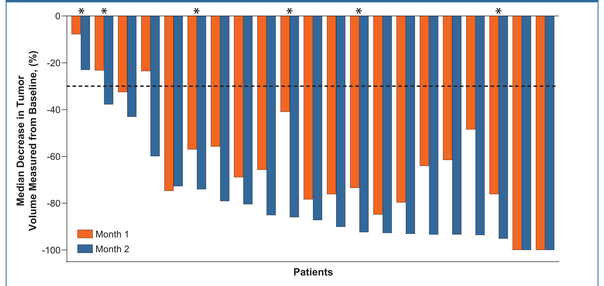
- Tumor response rate measured by MRI after 2 months of treatment was 90%; 2 (10%) patients had complete response, 17 (81%) had partial response, and 2 (10%) had stable disease; no patient experienced disease progression during the study period (**Figure 2**)
- Results measured by ultrasound were similar, with a 95% response rate after month 2 (**Figure 3**)

Figure 2. Decrease in Tumor Volume by MRI



*Indicates patients with hormone receptor-positive breast cancer.

Figure 3. Decrease in Tumor Volume by Ultrasound



*Indicates patients with hormone receptor-positive breast cancer.

- After 2 months of niraparib therapy, the median decrease in tumor volume by MRI and ultrasound was 86% and 87%, respectively

Safety

- Four patients had a dose reduction because of a treatment-emergent adverse event (TEAE): 3 neutropenia events, 1 thrombocytopenia event
- No patient discontinued treatment as a result of a TEAE
- Drug-related TEAEs are shown in **Table 3**

Table 3. Drug-Related TEAEs

Preferred term, n (%)	Total (N=21)
Any grade TEAEs*	
Nausea	13 (62)
Fatigue	10 (48)
Anemia	5 (24)
Decreased appetite	4 (19)
Insomnia	4 (19)
Neutrophil count decreased†	3 (14)
White blood cell count decreased	3 (14)
Grade ≥3 TEAEs	
Anemia	3 (14)
Neutropenia	2 (10)
Neutrophil count decreased	2 (10)
Hypertension	1 (5)
Thrombocytopenia	1 (5)

*Reported in >10% of patients receiving niraparib. †Neutropenia was reported in 2 (10%) patients.
TEAE=treatment-emergent adverse event.

Conclusions

- Niraparib showed promising antitumor activity in the neoadjuvant treatment of patients with localized HER2-negative, *BRCA*-mutated breast cancer
- Niraparib was well tolerated and showed low incidence of any grade and grade ≥3 hematologic toxicities
- A future analysis exploring the association between niraparib tumor accumulation and change in tumor size is planned

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Data Sharing Statement

Anonymized individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com.

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