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Clinical Confirmation of Higher Exposure to Niraparib in Tumor vs Plasma in Patients with Breast Cancer

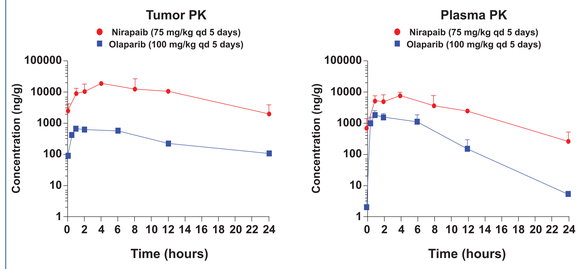
Laura Spring,[1] Ming Shan,[2] Minetta C. Liu,[3] Erika Hamilton,[4] Cesar A. Santa-Maria,[5] Hanna Irie,[6] Steven Isakoff,[1] James Reeves,[7] Leif W. Ellisen,[1] Andre Liem,[8] Adriana Mililo Naraine,[9] Julie Nangia,[10] David Page,[11] Peng Pan,[2] Kaiming Sun,[2] Julie R. Graham,[2] Sebastien Hazard,[2] Hyo Han[12]

[1]Massachusetts General Hospital, Boston, MA, USA; [2]TESARO: A GSK Company, Waltham, MA, USA; [3]Mayo Clinic, Rochester, MN, USA; [4]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA; [5]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA; [6]Icahn School of Medicine at Mount Sinai, New York, NY, USA; [7]Florida Cancer Specialists-South, Fort Myers, FL, USA; [8]Pacific Shores Medical Group, Long Beach, CA, USA; [9]Memorial Healthcare System, Hollywood, FL, USA; [10]Baylor College of Medicine, Houston, TX, USA; 11Providence Portland Medical Center, Portland, OR, USA; 12Moffitt Cancer Center-McKinley Outpatient Clinic, Tampa, FL, USA

Background

- Niraparib is a selective oral poly(ADP-ribose) polymerase 1/2 inhibitor approved as maintenance treatment for patients with recurrent ovarian cancer who are in complete or partial response to platinum-based chemotherapy[1,2]
- Animal models revealed unique pharmacological properties of niraparib, including higher concentrations in tumors than in plasma (**Figure 1**)[3,4]
  - Higher niraparib tumor concentrations were associated with improved tumor control[4]
- Another poly(ADP-ribose) polymerase 1/2 inhibitor, olaparib, has demonstrated lower tumor concentration compared with plasma in preclinical and clinical studies[4,5]

Figure 1. Steady-State Pharmacokinetics (PK) of Niraparib and Olaparib[4]



PK=pharmacokinetics; qd=once daily.

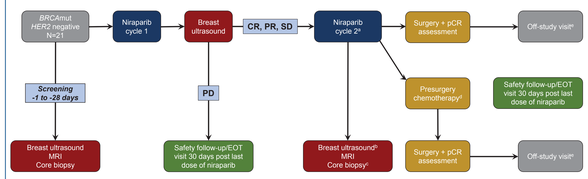
Objective

- To analyze intra-tumoral niraparib concentration and compare niraparib tumor and plasma concentrations in patients with breast cancer

Methods

- Samples were collected from patients enrolled in an ongoing pilot study evaluating the antitumor activity and safety of niraparib as neoadjuvant treatment for *HER2*-negative, *BRCA*-mutated localized breast cancer (NCT03329937)
- Patients received oral niraparib 200 mg once daily for at least two 28-day cycles (**Figure 2**)
- Tumor biopsies and plasma samples were obtained at the end of the second treatment cycle
  - At the time of this analysis, samples were available from 14 of the 21 enrolled patients
  - Tumor biopsies could not be collected from patients who did not have adequate tumor tissue (eg, those with complete or near-complete responses due to a lack of tumor tissue)
- Additional plasma samples were collected on cycle 2/day 1 at 0, 2, and 4 hours post-dose to determine steady-state maximum concentration (C_{max})
  - We used C_{max} to conservatively estimate the niraparib tumor/plasma ratio for those patients with missing matched plasma samples
- Niraparib concentrations in plasma and tumor samples for each patient were determined using qualified liquid chromatography–tandem mass spectrometry methods

Figure 2. 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 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 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 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

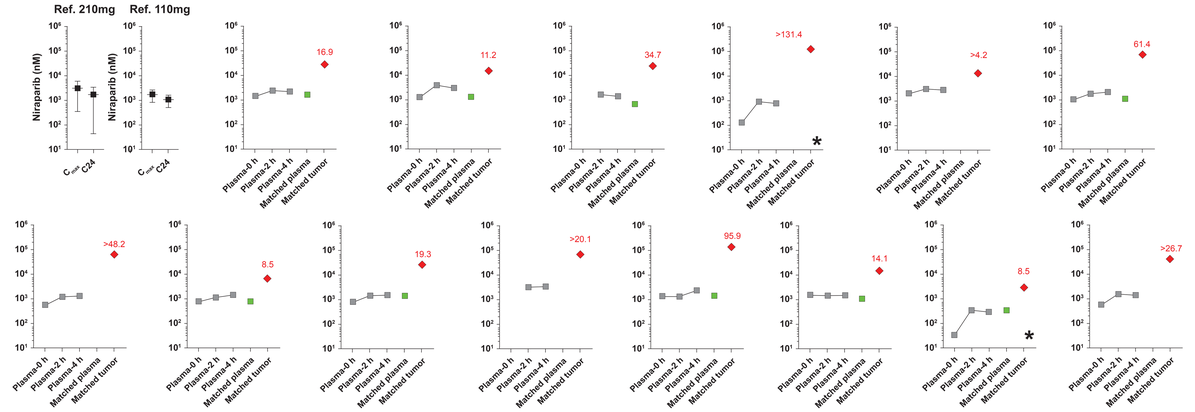
- Patient demographics and baseline characteristics are shown in **Table 1**.

Table 1. Patient Demographics and Baseline Characteristics

Characteristics	Total (n=14)
Age, years	
Median	39.5
Mean	42.3
Min, max	21, 73
Age group, n (%)	
<65 years	12 (85.7)
≥65 years	2 (14.3)
ECOG performance status score, n (%)	
0	13 (92.9)
1	1 (7.1)
Stage at diagnosis, n (%)	
I-II	12 (85.7)
III	2 (14.3)
***BRCA* mutation status, n (%)**	
BRCA1	10 (71.4)
BRCA2	3 (21.4)
BRCA1* and *BRCA2	1 (7.1)
Hormone receptor status, n (%)	
TNBC	11 (78.6)
ER and/or PR positive disease	3 (21.4)

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

Figure 3. Niraparib Plasma and Tumor Concentrations in Individual Patients



Niraparib concentration in patient tumor vs plasma samples (at C2D1 0, 2, and 4 h and C2D28 sample collection). Red data points represent individual patients' fold change in niraparib tumor concentration compared with time-matched plasma concentration (green). If the time matched plasma sample (green) is missing, we compared the tumor concentrations with C_{max} determined by the 0, 2, and 4h plasma concentration. This is a conservative estimate of tumor/plasma fold difference meaning the data presented is likely underestimating the actual value.
*Two patients in the analysis had a dose reduction to 100 mg before the end of cycle 2.

Table 2. Niraparib Concentrations in Plasma and Tumor

Patient number	Highest plasma niraparib concentration in C2D1 2-4 h post-dose (C_{max1} nM)	Niraparib concentration from C2D28 plasma collected with tumor (nM)	Niraparib concentration from C2D28 tumor (nM)	Tumor: plasma ratio
1	2596.80	1804.03	30493.70	16.9
2	4369.62	1485.67	16604.56	11.2
3	1825.88	752.20	26124.08	34.7
4*	923.86		121413.01	>131.4
5	3152.37		13296.13	>4.2
6	2094.30	1123.62	68977.57	61.4
7	1463.82		70538.15	>48.2
8	1635.49	867.68	7397.14	8.5
9	1585.55	1370.19	26498.62	19.3
10	3495.70		70226.03	>20.1
11	2359.59	1448.22	138891.49	95.9
12	1498.16	1061.19	14950.34	14.1
13*	346.45	340.21	2883.95	8.5
14	1510.64		40262.93	>26.7

Tumor:plasma ratio represents the fold difference between the intra-tumor concentration of niraparib and the plasma concentration
*These two patients had a dose reduction to 100 mg before the end of cycle 2.
C_{max}=maximum concentration.

- Niraparib concentrations in tumors ranged from 46325 ± 42360 nM (mean ± SD), which is 35.8 ± 35.9 (mean ± SD)-fold higher than those in corresponding plasma samples after 2 months of niraparib treatment (**Figure 3** and **Table 2**)
  - Niraparib concentrations in plasma were within the reference range previously reported for a 210 mg daily dose in patients with solid tumors (steady-state C_{max} 3160 ± 2799 nM, trough concentration (C_{trough}) 1753 ± 1707 nM, mean ± standard deviation [SD])[6]

Conclusions

- These results provide the first data of the intra-tumor concentration of niraparib in the clinical setting
- The concentration of niraparib was on average ~36-fold greater in tumor tissue than in plasma
- Confirms preclinical data that showed that tumor concentration is higher than in plasma, a unique property of niraparib
- Efficacy results will be reported at a future meeting

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Acknowledgments

The authors thank the patients and their families for their participation in this study, as well as the study teams at each of the study sites. Writing and editorial support, funded by TESARO: A GSK Company (Waltham, MA, USA) and coordinated by Teodor G. Paunescu, PhD, of TESARO, were provided by Eric Scocchera, PhD, and Frederique H. Evans, MBS, of Ashfield Healthcare Communications (Middletown, CT, USA) and Adrienne M. Schreiber of TESARO.

Disclosures

Laura Spring reports no conflicts of interest. Activate QR code for a complete list of author disclosures.

Presented at the ESMO Congress 2019 | September 27 – October 1, 2019 | Barcelona, Spain

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