Correlation Between Presence of Circulating Tumor DNA and Response to Neoadjuvant Niraparib in HER2-Negative, BRCA-Related Breast Cancer

Poster No. P5-13-21

Background

- An estimated 20%-30% of women diagnosed with breast cancer (BC) will develop recurrence after primary treatment.
- Robust biomarkers to predict the risk of early recurrence are needed.
- Circulating tumor DNA (ctDNA) may be a potential biomarker for predicting risk of recurrence and response to therapy in the neoadjuvant setting, such as with trastuzumab.
- Analyses of ctDNA may be a potential biomarker for predicting risk of recurrence and response to therapy in the neoadjuvant setting, such as with trastuzumab.
- Mutations in TP53 occur in 30%-50% of invasive primary BC cases, and may be an effective biomarker in BC due to this high prevalence.
- Niraparib, a poly(ADP-ribose) polymerase (PARP)-1/2 inhibitor, provides a new, effective treatment option for BRCA1/2-mutated (BRCAm) early-stage BC after neoadjuvant/adjuvant chemotherapy and advanced/metastatic BC.

A pilot study evaluated niraparib in the neoadjuvant setting (NCT0339937) in female patients with human epidermal growth factor receptor 2 (HER2)-negative, BRCAm BC.
- All 18 response-evaluable patients had a clinical response after 2 months of treatment by at least one imaging modality.
- Grade ≥3 treatment-related treatment-emergent adverse events (TEAEs) occurred in 7 (33.3%) patients; no discontinuations occurred due to TEAEs.
- Exploratory analyses were performed, applying tumor genotyping of peripheral blood from participating patients to examine the clinical utility of ctDNA as a marker for predicting the likelihood of achieving pCR.
- Targeted next-generation sequencing (NGS) of ctDNA was also used to test for potential mutations of interest.

Methods

Study Design
- Exclusion and inclusion criteria have been previously described.
- Patients received niraparib 200 mg orally once daily, for 28 days for 3 cycles, with the potential to administer 4 more cycles (up to 6 cycles maximum).

Subanalysis assessments

Imaging
- Magnetic resonance imaging (MRI) and ultrasound imaging were performed at screening (Day 1), the end of Cycle 1 (Day 8) and Day 28 (ultrasound only) at the end of CDDP; subsequent cycles had ultrasound imaging only if applicable.
- Tumor responses were determined by MRI (primary endpoint) and ultrasound (secondary endpoint).
- Blood samples collected.
- Blood samples were collected from all 21 patients who enrolled in the study.
- Tumor screening: CDDP, CDDP, and psoriasis.
- Plasma was extracted from blood samples within 4 hours of collection and stored at 20°C according to the manufacturer’s collection procedures.

Resolution ctDNA-homogeneous recombination repair (HRR) NGS assay
- Targeted NGS analysis of ctDNA was carried out using a proprietary target capture and analysis pipeline described previously by Paweluk CP, et al. Clin Cancer Res 2015; 21:7167-7178 employing a custom panel of probes across 33 genes of interest that are potentially implicated in DNA repair and cancer.
- TP53 mutation was detected using probes covering the coding region of TP53.

Data analysis
- The sample was considered ctDNA-positive if any somatic mutation was detected by the ctDNA-HRR NGS assay (Resolution Bioscience).
- The detection of TP53 somatic mutations was defined as a MAF ≥0.365.
- The Mann–Whitney test was used for correlation of ctDNA and tumor volume and a Kruskal–Wallis test was used for correlation between TP53 MAF and baseline tumor stage.

Results

Correlation between presence of ctDNA and tumor volume
- ctDNA was detected at screening in 10/21 patients enrolled (47.6%) and was associated with a larger tumor volume (Figure 1).
- ctDNA-positive samples correlated with a larger tumor volume by ultrasound at baseline compared with ctDNA-negative samples (mean [standard deviation]: 17825.39 mm3 (16683.19) and ctDNA-negative: 1761.05 mm3 (166.42); P = 0.0001

Figure 1. Association of ctDNA detection and tumor volume by ultrasound

Table 1. Baseline TP53 MAF association with disease stage and subtype

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Correlation between TP53 MAF and tumor volume after niraparib treatment over time
- Correlation between detectable TP53 MAF and tumor volume following treatment with niraparib was assessed in 11/21 (52.4%) patients individually over time (Figure 3).
- Overall, decrease of detectable TP53 MAF from baseline (mean [SD] = 0.09 [0.11] median and p < 0.12) did not persist to prophylaxis (mean [SD] = 0.01 [0.02]).
- A subset of patients achieved detectable depletion of detectable TP53 MAF and persistent shrinkage in tumor volume without rebounding (Figure 3; patients 11, 15, 18, and 20).
- 6 patients had >90% tumor volume decreases (confirmed by MRI or ultrasonography) at C2D28, 5 of which had sustained TP53 MAF depletion (Figure 3; patients 11, 15, 18, 19, and 20).
- Of the 8 patients who achieved pCR in the study, 3 had detectable ctDNA (patients 14, 15, and 20); of the 2, this had sustained TP53 MAF depletion (data unavailable for patient 14).
- The remaining 5 patients achieving pCR had no detectable ctDNA at baseline due to smaller tumor size.
- A subset of patients (14, 15, and 19) had less robust tumor responses, 2 of which had increased TP53 MAF levels pre-surgery (Figure 3).

Figure 3. Patient-level correlations between TP53 MAF and tumor volume following niraparib treatment over time

Conclusions
- Here we demonstrate the potential utility of TP53 MAF detection to monitor response to neoadjuvant niraparib treatment.
- Presence of TP53 MAF (11/21 [52.4%]) demonstrated an observed trend of association with both larger tumor volume as well as more advanced disease at baseline.
- Longitudinal analysis revealed a correlation between TP53 MAF depletion and decrease in tumor volume following treatment with niraparib.
- Further research is warranted to understand the lack of association between presence of ctDNA with clinical outcomes, such as pCR, and disease recurrence.
- ctDNA surveillance has the potential to guide treatment regimens and provide effective personalized therapy in BC.

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References


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