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

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*At the time of the study, author was a GSK employee.

Background

- An estimated 20%–30% of women diagnosed with breast cancer (BC) will develop recurrence after treatment[1]
  - 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 pathological complete response (pCR)[2]
  - Mutations in *TP53* occur in 30%–35% of invasive primary BC cases, and may be an effective biomarker in BC due to this high prevalence[3]
- Niraparib, a poly(ADP-ribose) polymerase (PARP)-1/2 inhibitor, provides a new, effective treatment option for *BRCA*1/2-mutated (*BRCA*m) early-stage BC after neoadjuvant/adjuvant chemotherapy and advanced/metastatic BC[4,5]
- A pilot study evaluated niraparib in the neoadjuvant setting (NCT03329937) in female patients with human epidermal growth factor receptor 2 (HER2)-negative, *BRCA*m BC[5]
  - 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

Aim

To characterize the relationship between ctDNA and tumor response, with a focus on circulating *TP53* mutant allelic frequency (MAF) in patients with HER2-negative, *BRCA*m BC treated with neoadjuvant niraparib

Methods

Study Design

- Exclusion and inclusion criteria have been previously described[5]
  - Patients received niraparib 200 mg orally once daily, given for 28 days for 2 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 (C) 1 Day (D) 28 (ultrasound only) the end of C2D28; subsequent cycles had ultrasound imaging only if applicable
  - Tumor responses were determined by MRI (primary endpoint) and ultrasound (secondary endpoint)

Blood sample collection

- Blood samples were collected from all 21 patients who enrolled in the study
  - Time points: screening, C1D28, C2D28, and presurgery
  - Plasma was extracted from blood samples within 4 hours of collection and stored at -20°C according to the manufacturer's collection procedures

Resolution ctDx-homologous recombination repair (HRR) NGS assay

- Targeted NGS analysis of ctDNA was carried out using a proprietary target capture and analysis pipeline described previously by Paweletz CP, et al. *Clin Cancer Res* 2016,[6] employing a custom panel of probes across 33 genes of interest that are potentially implicated in DNA repair and cancer
  - *TP53* MAF was detected using probes covering the coding region of *TP53*[6]

Data analysis

- The sample was considered ctDNA-positive if any somatic mutation was detected by the ctDx™ HRR NGS assay (Resolution Bioscience)
  - The detection of *TP53* somatic mutations was defined as a MAF ≤0.365

Statistical analysis

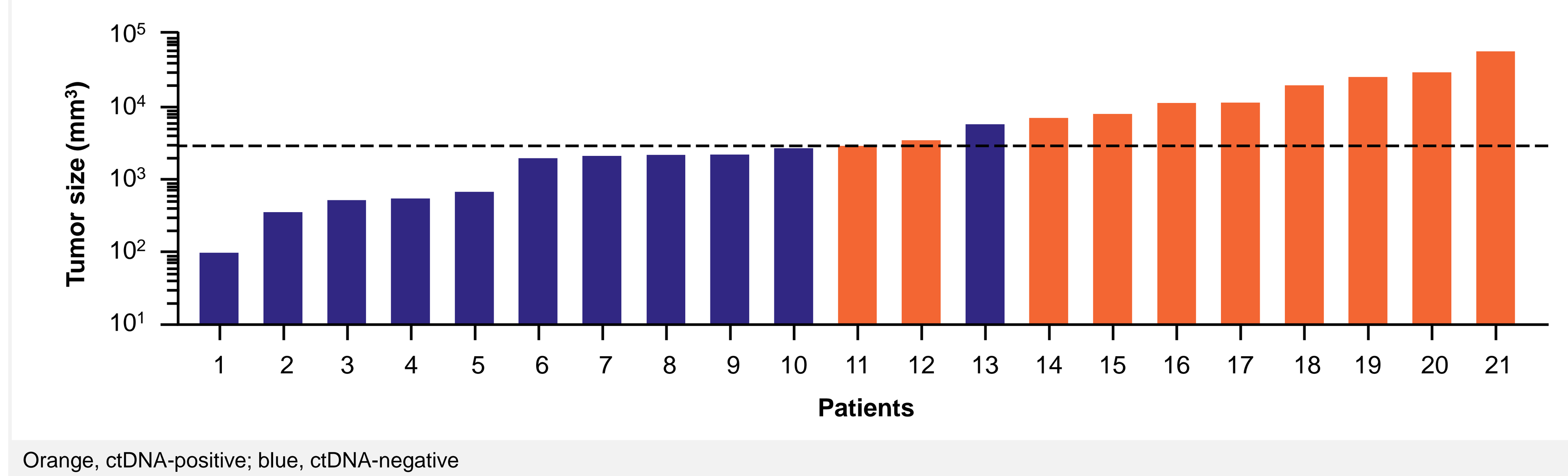
- The Mann–Whitney test was used for correlation of ctDNA and tumor volume and a Kruskal–Wallis test was used for correlation between *TP53* MAF and baseline tumor stage

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; StdDev])
  - ctDNA-positive: 17825.39 mm³ (16803.19) and ctDNA-negative: 1761.05 mm³ (1650.42); P<0.0001

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



Orange, ctDNA-positive; blue, ctDNA-negative

TP53 MAF association with tumor stage and tumor volume

- *TP35* MAF was detected in 10/21 (47.6%) patients at screening
- Linear regression modeling showed a positive correlation between tumor volume by ultrasound and *TP53* MAF at baseline (R^2=0.206, P=0.0386)
- Across all 21 patients, there was a correlation between *TP53* MAF and baseline tumor stage (T; **Figure 2**)
  - Mean (StdDev), T1 0 (0), T2 0.05 (0.09), and T3 0.21 (0.12); P=0.005
- Presence of baseline *TP53* MAF also appeared to be associated with more advanced disease stages, and was more prevalent in the triple-negative breast cancer (TNBC) subtype compared with the hormone receptor (HR)-positive subtype (**Table 1**)

Figure 2. Correlation between *TP53* MAF and baseline tumor score

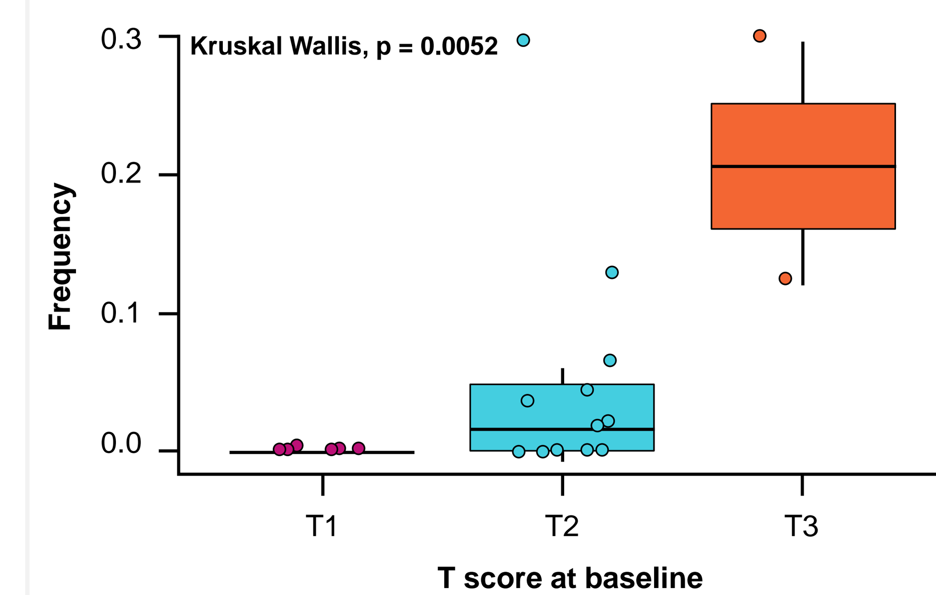


Table 1. Baseline *TP53* MAF association with disease stage and subtype

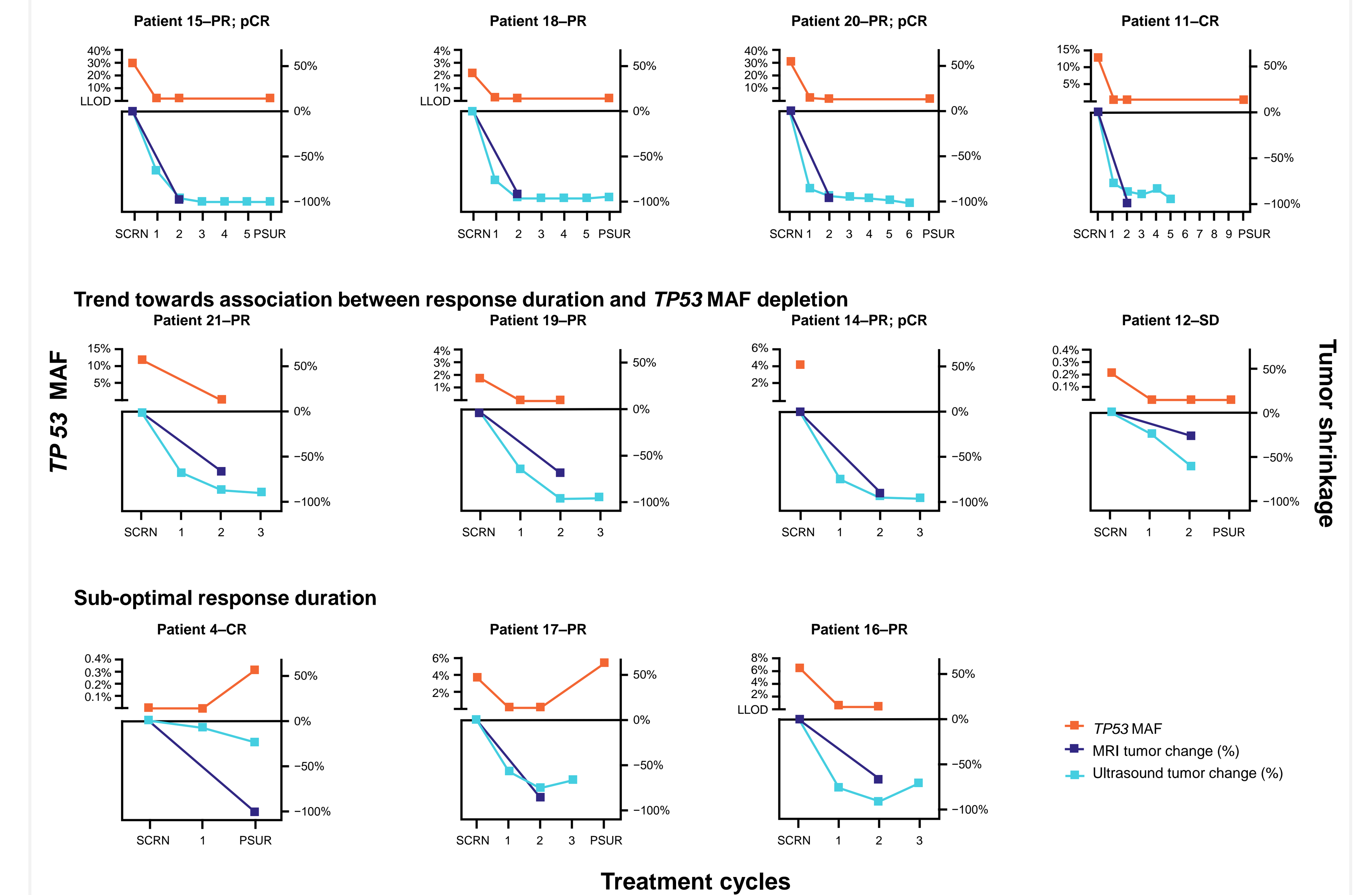
TP53 MAF	Disease Stage (I–III)			Disease Subtype	
	Stage I (n=8)	Stage II (n=10)	Stage III (n=3)	HR-positive (n=6)	TNBC (n=15)
Mean (StdDev)	0.01 (0.02)	0.07 (0.12)	0.10 (0.05)	0.02 (0.02)	0.06 (0.10)

n, number

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 [StdDev], 0.09 [0.11]) was evident by C1D28 of neoadjuvant niraparib treatment (mean [StdDev], 0.0 [0.0]) and persisted to presurgery (mean [StdDev], 0.01 [0.02])
- A subset of patients achieved 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 these, 2 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 (patients 4, 16, and 17) had less robust tumor responses, 2 of which had increased *TP53* MAF levels presurgery (**Figure 3**)

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



Clinical responses by MRI at Cycle 2 and pCR are shown; pCR is patients defined as defined as *ypT0/Tis ypN0* by receipt of pre operative chemotherapy
CR, complete response; LLOD, lower limit of detection; PR, partial response; PSUR, pre-surgery; SCRN, screening; SD, stable disease

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 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

Disclosures

MS has no conflicts to report and is an employee of GSK. **LS** reports consultant/advisory board to Novartis, Avrobio, and Puma Biotechnology; research funding to institution Tesaro, Merck. **MCL** reported nonfinancial support from Celgene, Merck, and Pfizer. **EH** reports consulting fees paid to institution only (no personal fees) from Pfizer, Genentech/Roche, Lilly, Puma Biotechnology, Daiichi Sankyo, Dantari, Merck, CytomX, H3 Biomedicine, Arvinas, Deciphera Pharmaceuticals, Eisai, Mersana Therapeutics, Boehringer Ingelheim, AstraZeneca, Novartis, Silverback Therapeutics, Black Diamond, and Seagen; research/clinical trial support paid to institution only (no personal fees) from Curis, Verastem, Zymeworks, Syndax, Lycera, Rgenix, Novartis, Mersana, Millenium, TapImmune, Lilly, OncoMed, Genentech/Roche, Pfizer, Tesaro, Boehringer Ingelheim, Sermonix Pharmaceuticals, H3 Biomedicine, Infinity Pharmaceuticals, Acerta, Takeda, Macrogenics, AbbVie, Immunomedics, Fujifilm, Effector, Merus, Nucana, Regeneron, Leap Therapeutics, Taiho Pharmaceutical, EMD Serono, Daiichi Sankyo, ArQule, Syros, Clovis, Cytomx, InvestisBio, Deciphera, Onconova, Dana Farber Cancer Hospital, Sutro, Hutchinson, Zenith Epigenetics, Arvinas, Torque, Harpoon, Fochon, Black Diamond, Orinove, Molecular Templates, Silverback Therapeutics, Compugen, G1 Therapeutics, Karyopharm Therapeutics, Torque Therapeutics, MedImmune, SeaGen, Puma, Biotechnology, Fochon, StemCentRx, Radius Health, AstraZeneca, Merck, PharmaMar, Olema, Polyphor, Immunogen, Plexxicon, Amgen, Akesobio Australia, and Shattuck Labs. **HI** has no conflicts to disclose. **CAS-M** reports research funding from Pfizer, AstraZeneca, and Tesaro; and has served on advisory boards for BMS, Genomic Health, Polyphor, Halozyme, Athenex, and Seattle Genetics. **SJI** reports consultant/advisory roles for AbbVie, PharmaMar, Genentech/Roche, Myriad Genetics, Hengrui Therapeutics, Puma Technology, and Immunomedics; institutional research funding from Genentech, PharmaMar, AbbVie, OncoPep, Merck, and AstraZeneca/MedImmune; travel support from PharmaMar. **JR** has no conflicts to disclose. **LWE** is supported for this work by grants from the Gray Foundation Team Science Program and the Ludwig Center at Harvard. **LPL** has no conflicts to disclose. **KG** and **CB** are employees of Resolution Bioscience (part of Agilent), **BF**, **HZ**, and **EH** are employees of GSK. **KS** and **JRG** were previous employees of GSK. **HH** reports speaker's honorarium from Lilly Pharmaceuticals, research funding from Arvinas, AbbVie, Daiichi Pharma, G1 therapeutics, GSK, Marker therapeutics, Novartis, Pfizer, Seattle Genetics, Prescient, Horizon, and Karyopharm, Seagen, and Zymeworks.

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