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THE POWER OF SHARED PURPOSE: Transforming Gynecologic Cancer Care

PARPi response monitoring using personalized circulating tumor DNA testing in patients with ovarian cancer

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Background

- Recurrence rates in ovarian cancer (OC) patients remain high after curative-intent treatment including surgery and adjuvant treatment (AT).[1]
- The recent incorporation of polyADP-ribose polymerase inhibitors (PARPi's) as maintenance therapy has shown a reduction in relapse rates and improved survival.[2] However, a predictive biomarker to reliably assess response to therapy is lacking.
- We sought to evaluate circulating tumor DNA (ctDNA) as a predictor of clinical outcomes in patients with OC receiving PARPi therapy.

Methods

- This was a real-world evidence study evaluating ctDNA in patients with OC receiving PARPi therapy. Longitudinal plasma samples (n=156) were collected from 45 patients (pre-PARPi-within 1.5 months from initiation of therapy, N=7), during-PARPi (N=41), and post-PARPi (within 6 months of therapy completion, N=23). Complete patient and tumor information is shown in **Table 1**.
- Retrospective ctDNA analysis was performed using a clinically validated, personalized, tumor-informed 16-plex PCR assay (Signatera™, Natera Inc.). The association between ctDNA status and patients' clinical outcomes was evaluated. Patients were followed clinically for a median follow-up of 16.8 months (range: 3.6-66.6).

Table 1. Patient and tumor characteristics (N=45)

Parameter	# Patients (%)
Stage	
I	2 (4.4%)
II	9 (20%)
III	21 (46.7%)
IV	10 (22.2%)
unknown	3 (6.7%)
Histology	
Serous	35 (77.8%)
Clear cell	3 (6.7%)
Mixed	1 (2.2%)
Poorly differentiated	1 (2.2%)
unknown	5 (11.1%)
BRCA Status	
Negative	21 (46.7%)
Positive	11 (24.4%)
unknown	13 (28.9%)
HRD Status	
Deficient	16 (35.5%)
Proficient	12 (26.7%)
unknown	17 (37.8%)

References

1. Garzon S, et al. *Gland Surg.* 2020 Aug; 9(4): 1118–1129. doi: 10.21037/gs-20-3252.
2. Wiggans A, et al. *Cochrane Database Syst Rev.* 2022 Feb 16. doi: 10.1002/14651858.CD007929.pub4

Acknowledgments and Disclosures

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Tumor-informed longitudinal ctDNA monitoring predicts outcomes in patients with ovarian cancer undergoing PARPi maintenance therapy

Figure 1. Patient overview plots

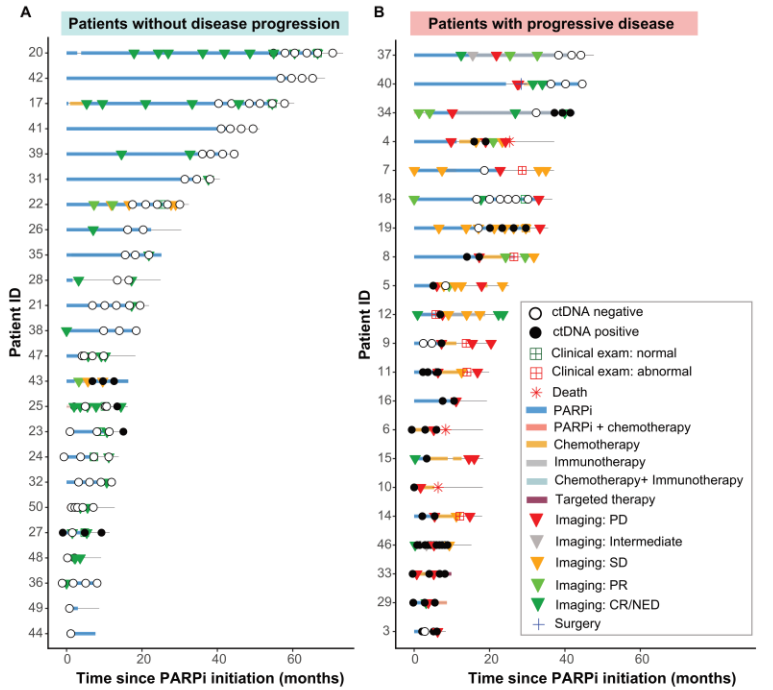

Figure 1. Patient overview plots showing longitudinal ctDNA analysis, treatment timeline, and imaging results for 45 patients. **A.** Patients without disease progression (N=24). **B.** Patients who had progressive disease (N=21). **Abbreviations:** ctDNA, circulating tumor DNA; CR, Complete response; NED, No evidence of disease; PD, Progressive disease; PR, Partial response; PARPi, polyADP-ribose polymerase inhibitors; SD, Stable disease.

Figure 2. ctDNA detection rates, Sankey plot, Patient-specific clinical disease trajectories, and Survival probability

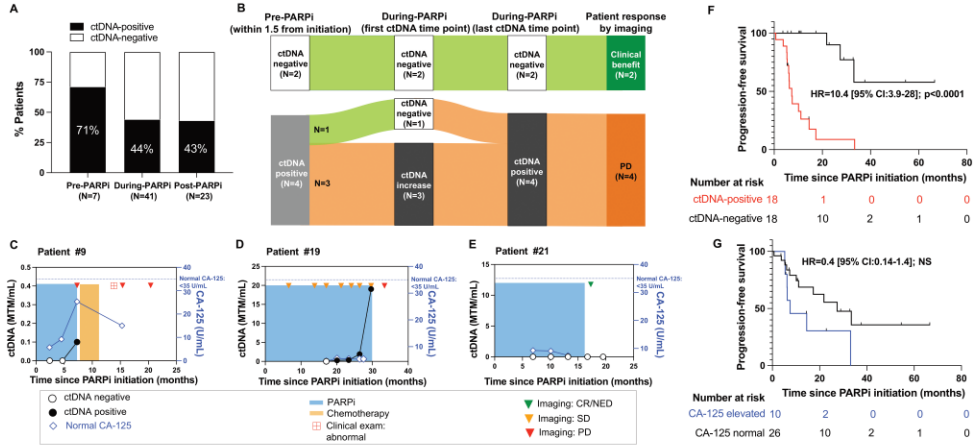

Figure 2. A. Bar plots showing ctDNA detection pre-PARPi (within 1.5 months from initiation), during-PARPi, and post-PARPi (within 6 months from completion). **B. Sankey Plot:** Of 7 patients who had ctDNA testing pre-PARPi, 6 had subsequent testing performed and were included in this analysis. Patients who were ctDNA negative (N=2) prior to PARPi initiation (pre-PARPi) remained ctDNA negative during therapy and had corresponding clinical benefit (NED) on imaging. Patients who were ctDNA positive (N=4) pre-PARPi who either experienced an increase or transient clearance in ctDNA were ctDNA positive at the last follow-up consistent with PD on imaging. Median time from pre-treatment to the beginning of PARPi was 0.7 months (range: 0.2-1.2). Median for the first ctDNA time point on PARPi was 2.9 months (range: 1.5-3.7). Median for last ctDNA time point on PARPi was 4.4 months (range: 2.8-8.1). **C-E. Patient-specific plots. C. Patient #9** tested ctDNA-negative on treatment. Post-treatment completion, plasma levels showed detectable ctDNA, consistent with PD on imaging. CA-125 remained at normal levels throughout PARPi therapy. **D.** Following an initial negative ctDNA test, **Patient #19** showed a persistent increase in ctDNA levels during-PARPi therapy, coinciding with SD and eventually PD on imaging. CA-125 remained at normal levels throughout PARPi therapy. **E. Patient #21** tested serially ctDNA-negative during-PARPi therapy with CR/NED observed via radiologic imaging. **Kaplan-Meier estimates** demonstrating the association of ctDNA (**F**) and CA-125 (**G**) status with PFS (N=36). **F.** Patients who were any time ctDNA-positive during-PARPi had a significantly reduced PFS compared to their negative counterparts (HR=10.4; p<0.0001). **G.** In contrast, elevated CA-125 levels any time during-PARPi were not associated significantly with PFS. **Abbreviations:** HR, Hazard ratio; CI, Confidence interval; CR, Complete response; MTM/mL, Mean Tumor Molecules/mL of plasma; NED, No evidence of disease; NS, not significant; PFS, progression-free survival; PARPi, polyADP-ribose polymerase inhibitors; PD, progressive disease; U, units.

Conclusions

- ctDNA status using a tumor-informed assay during-PARPi was predictive of treatment response. A rise in ctDNA levels during-PARPi was strongly associated with progressive disease. Similarly, serially undetectable ctDNA was associated with favorable clinical outcomes.
- Detectable ctDNA but not elevated CA-125 was significantly associated with inferior PFS (HR=10.4; p<0.0001 and HR=0.4; NS, respectively).
- In this cohort, ctDNA levels were more predictive than CA-125 during PARPi therapy, suggesting ctDNA could serve as a valuable tool for monitoring patients with ovarian cancer undergoing PARPi maintenance therapy.