ctDNA in treatment response monitoring in patients with relapsed gynecologic malignancies

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Background

- The role of immunotherapy in gynecologic malignancies continues to evolve. Use of immunotherapy (IO)/ immune checkpoint blockade (ICB) agents have consistently demonstrated less than a 15% response rate in ovarian, cervical, and subsets of endometrial cancer.[1]
- Given the limited number of responders, a novel approach to treatment monitoring is needed to better sequence therapies.
- Circulating tumor DNA (ctDNA) surveillance in patients treated with IO/ICB is one such approach that has been shown to predict clinical benefit.[2,3]
- Utilizing ctDNA as a predictive biomarker, we sought to evaluate patients with recurrent gynecologic malignancies managed with ICB therapy.

Methods

- In this retrospective analysis of real-world data, plasma samples (n=132) from 25 patients with recurrent/metastatic ovarian (n=7), endometrial (n=12), and cervical (n=6) cancers were identified to have received ICB/IO therapy (Table 1).
- Complete clinical data was available for 12 patients.
- A personalized and tumor-informed multiplex PCR assay (Signatera™ bespoke mPCR NGS assay) was used for the detection of ctDNA in plasma samples (Figure 1).
- Serial time points were collected to monitor ctDNA levels in response to immunotherapy (Figure 2).

Figure 1. Signatera Molecular Protocol

Sequence tumor tissue to identify unique signature of tumor mutations

Custom design and manufacture personalized mPCR assay for each patient targeting clonal mutations found in tumor

Use personalized assay to test patient's blood for presence of circulating tumor DNA (ctDNA)

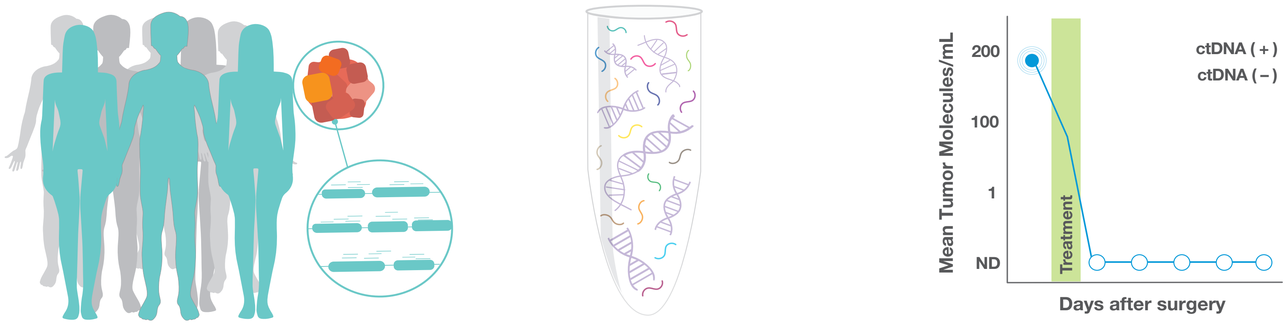

Table 1. Patient Demographics (N=25)

Recurrent Gynecologic Malignancies	# Patients (%)
Cervical cancer (n=6)	
Stage I/II	4 (67)
Stage III/IV	2 (33)
Endometrial cancer (n=12)	
Stage I/II	1 (8)
Stage III/IV	11 (92)
Ovarian cancer (n=7)	
Stage I/II	0 (0)
Stage III/IV	7 (100)

Of the 25 patients, 10 had ctDNA pre-IO ctDNA status available and of these 70% (7/10) were ctDNA-positive.

Figure 2. Patient overview plot (N=12), ctDNA dynamics during IO, and patient-specific plots

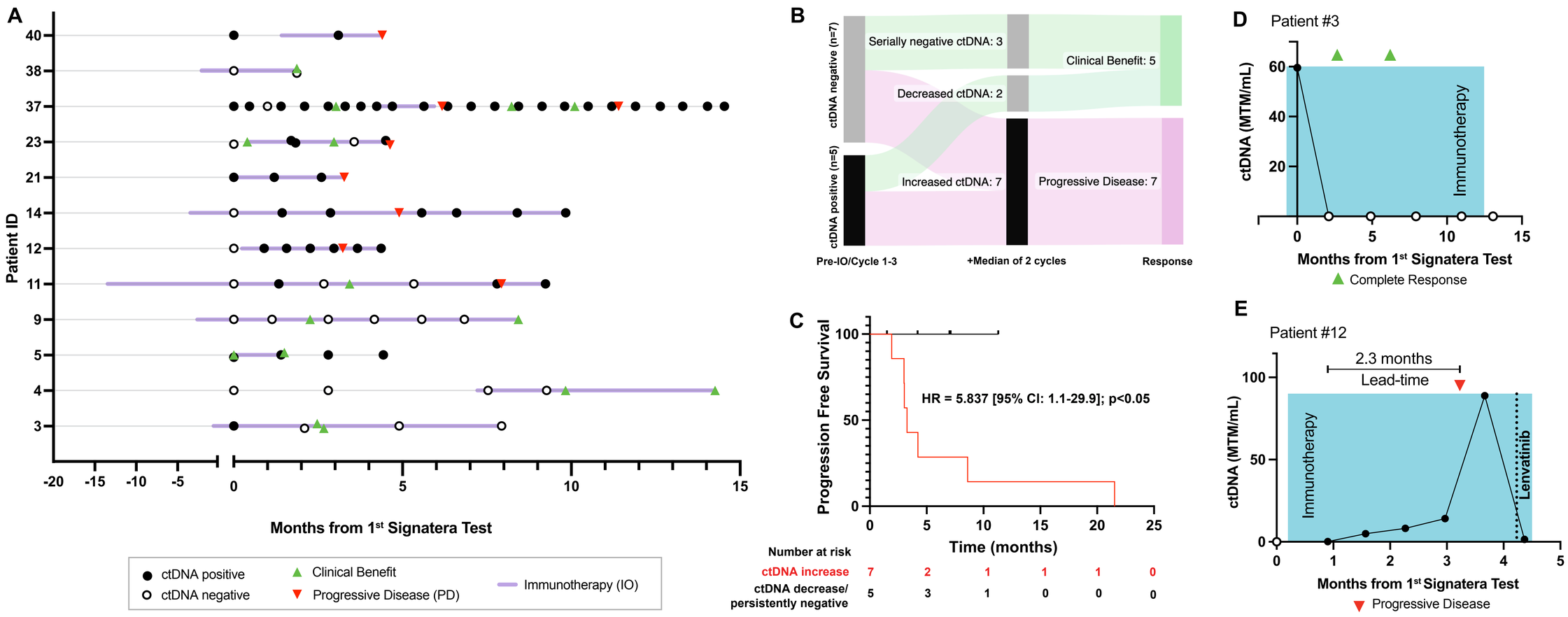

Figure 2: A. Patient overview plot: among 12 patients with recurrent gynecologic malignancies, ctDNA was detected in 42% (5/12) of patients at first timepoint. **B-C.** Early ctDNA dynamics during IO treatment were examined and correlated with patient response **B. Sankey plot:** of 12 patients, all 7 patients who progressed had increase in ctDNA and of 5 patients who achieved clinical benefit, 2 had ctDNA decrease and the remaining 3 were serially negative. **C. Kaplan-Meier plot:** early ctDNA dynamics during systemic therapy is associated with patient response. Patients who experienced increase in ctDNA (N=7) exhibited a lower Progression Free Survival (PFS) compared to patients who showed a ctDNA decrease or were persistently ctDNA-negative (N=5) (HR=5.837, 95% CI: 1.1-29.9, p<0.05). **D-E. Patient-specific plots:** ctDNA trajectories demonstrating a responder (Patient #3) and a non-responder (Patient #12). **D.** In Patient #3, ctDNA findings were in concordance with complete response as confirmed by two consecutive imaging events. **E.** In patient #12, ctDNA dynamics indicated disease progression 2.3 months ahead of radiologic imaging. Abbreviations: HR: hazard ratio; CI: confidence interval.

Conclusions

- We demonstrate a ctDNA detection rate of 70% (7/10) in the Pre-IO setting using a personalized, tumor-informed ctDNA assay.
- Early ctDNA dynamics during systemic therapy were associated with patient response (HR: 5.837, p<0.05).
- ctDNA monitoring during the course of immunotherapy for patients with recurrent gynecologic malignancies allows for accurate determination of therapeutic response and early prediction of disease progression.

References

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