Ultra-sensitive, tumor-informed ctDNA profiling in pembrolizumab-treated gastroesophageal cancer patients reveals longitudinal ctDNA kinetics

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BACKGROUND
Metastatic esophagogastric cancer (mEGC) is a lethal disease with poor long-term survival. Recent studies have established anti-PD-1 therapy in combination with chemotherapy as the standard of care for first-line therapy for mEGC. KeyLargo (NCT03342937 [1]) was a single-arm phase II study of pembrolizumab in combination with capecitabine and capecitabine in the first-line treatment of patients with HER2-negative mEGC. While high response rates were noted, not all patients received benefits, emphasizing the need for better biomarkers. Paired tumor biopsies and plasma were longitudinally collected, processed, and stored for optimal biomarker testing. In this retrospective study, we employed a novel, tumor-informed circulating tumor DNA (ctDNA) approach for longitudinal disease monitoring and dynamic tumor evolution.

OBJECTIVES
Investigate the application of ultra-sensitive ctDNA assay and explore ctDNA parts per million (PPM) as a prognostic biomarker for the clinical benefit of anti-PD-1 immunotherapy in combination with capecitabine and capcitabine in the first-line treatment of patients with HER2-negative mEGC.

RESULTS
Thirty-six patients were enrolled between January 2018 and January 2020. Twenty-five patients were analyzed for the presence and quantification of ctDNA in plasma. Responders for exclusion included the absence of FFPE blocks (n=4), poor DNA yields (n=5), and low tumor content (n=2). Out of these pts, the best overall response consisted of 2 complete response (CR), 14 partial response (PR), 2 stable disease (SD), and 5 progressive disease (PD) patients. Data was missing for two patients, specified as withdrew/non-evaluable (NE).

METHODS

Tracking patient response requires ultra-sensitive profiling
NeXT Personal detects a large spectrum of ctDNA-positive events, allowing for ultra-high sensitivity for low tumor fractions (<0.01%). The dynamic range of ctDNA-positive samples varied from 406,067 down to 1.5 ctDNA molecules PPM (Figure 2).

CONCLUSIONS
Molecular clearance and molecular response were highly prognostic for improved clinical outcomes
Lack of early molecular response (ctDNA decrease) was associated with worse overall survival (OS) and progression-free survival (PFS). Molecular clearance of ctDNA was associated with improved OS and PFS. To simulate what the ctDNA results would have been with an assay with a 100 PPM limit of detection, we re-analyzed our data, changing all of our positive detections at <=100 PPM to “not detected.” With this 100 PPM simulated LOD, clearance of ctDNA was no longer associated with improved OS (p = 0.68) and PFS (p = 0.37).

REFERENCES
• Ultra-sensitive ctDNA profiling is complementary to imaging, allowing for more granular assessment of patient response dynamics and tumor size.
• ctDNA profiling correlates with the patients’ best response and tumor size dynamics.
• Molecular PPM dynamics are prognostic of patient response to immunotherapy.


• Early-stage disease, an ultra-sensitive ctDNA platform is critically important for accurately tracking and predicting response to therapy.
• Ultra-sensitive ctDNA profiling correlates with the patients’ best response and tumor size dynamics.
• Molecular PPM dynamics are prognostic of patient response to immunotherapy.