Clinical utility of landmark ctDNA molecular response as an early indicator of immunotherapy outcomes in non-small lung cancer

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Introduction

Circulating tumor DNA (ctDNA) analyses are informative as an early indicator of immunotherapy (IO) response in advanced non-small cell lung cancer (NSCLC), however the clinical role of ctDNA molecular response requires further validation. We prospectively tested the clinical sensitivity of landmark ctDNA molecular response compared to two-timepoint definitions in predicting IO outcomes.

Approach

- As part of a prospective clinical protocol (NCT05995821), we performed ctDNA (n=328) and matched white blood cell DNA (WBC; n=109) targeted error-correction sequencing (Elio Plasma Complete, Labcorp) from 109 patients with metastatic NSCLC who received anti-PD-(L)1-containing therapies.
- Among 2,818 variants, 23% were clonal haematopoiesis-related.
- Following variant cellular origin resolution, landmark ctDNA molecular response (mR) was defined as undetectable ctDNA within 3-9 weeks of treatment initiation.
- Clinical benefit was assessed at 6 months from therapy start.
- Tumor whole exome sequencing-informed vs. WBC-informed vs. plasma-only approach was compared in 28 patients.

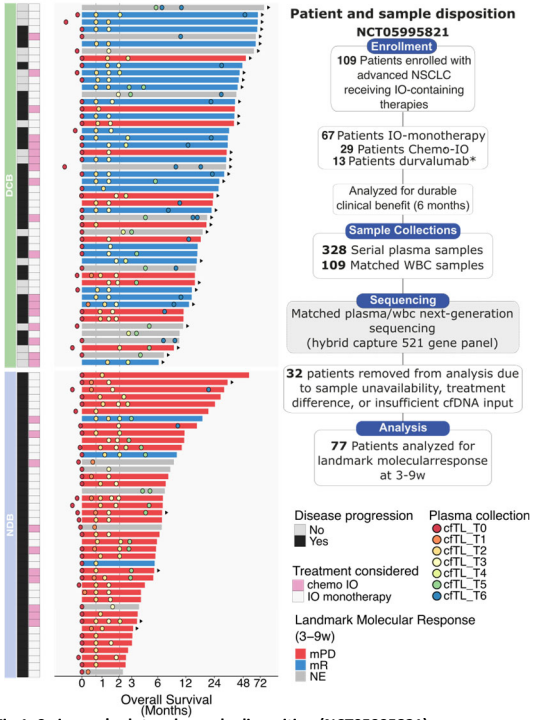

Fig.1. Swimmer's plot and sample disposition (NCT05995821).

Results

- The tumor-agnostic WBC-informed approach maximizes the number of evaluable cases with detectable ctDNA while maintaining the overall accuracy for mR, by striking a balance between sensitivity and specificity for clinical benefit prediction.

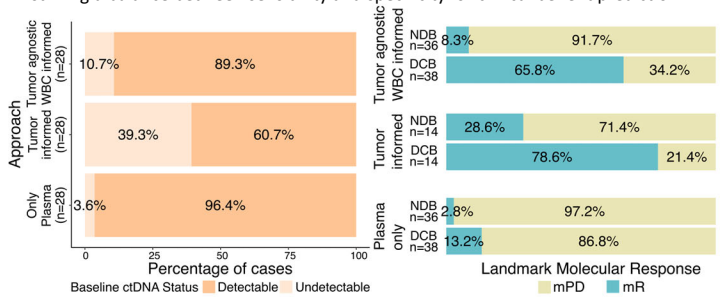

Fig.2. Differences in ctDNA detection and molecular response based on liquid biopsy approach.

- Single timepoint landmark molecular response determined at 3-9 weeks achieved high clinical specificity (91.7%) and sensitivity (65.8%) in predicting clinical benefit, showing similar performance to two-timepoint approaches.

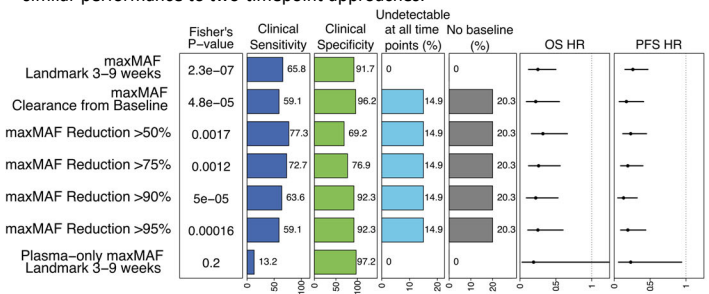

Fig.3. Clinical sensitivity of landmark vs. two-timepoint ctDNA molecular response.

- Patients with persistent ctDNA detection in ≥1 samples in the landmark interval had similar PFS to those with a single detectable sample.
- ctDNA detection at baseline did not correlate with a significant difference in PFS in either patients with detectable or ctDNA at the landmark timepoint.

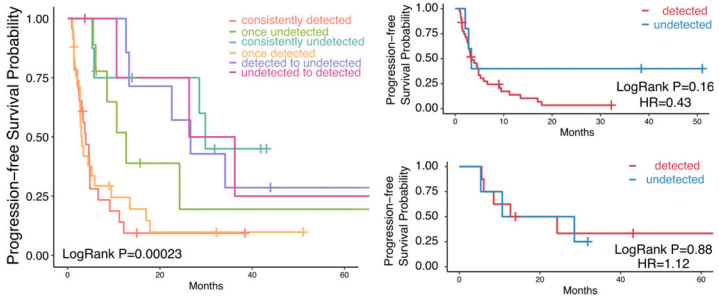

Fig.4. PFS differences by variable detection in the landmark window and by baseline ctDNA in mR.

- ctDNA mR was correlated with DCB in all patients and in the IO group.
- Patients with mR had significantly longer PFS (log rank p<0.001).

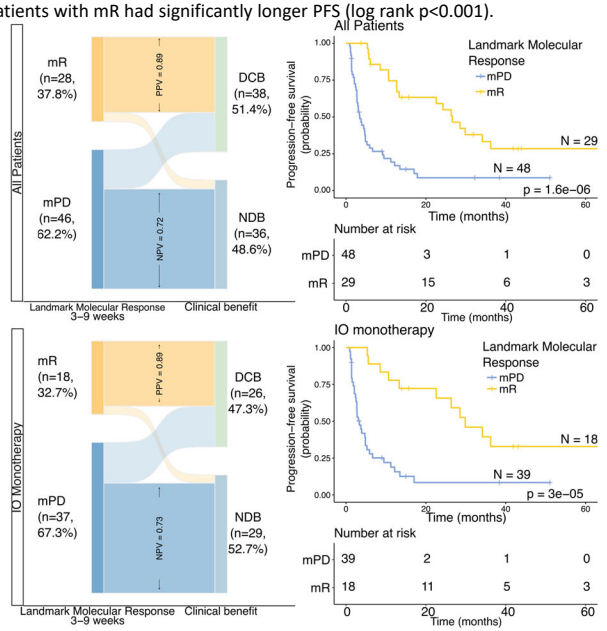

Fig.4. Molecular response is associated with durable clinical outcomes with immunotherapy

- Multivariate Cox regression analyses showed a significant independent association between landmark ctDNA molecular response and overall survival.

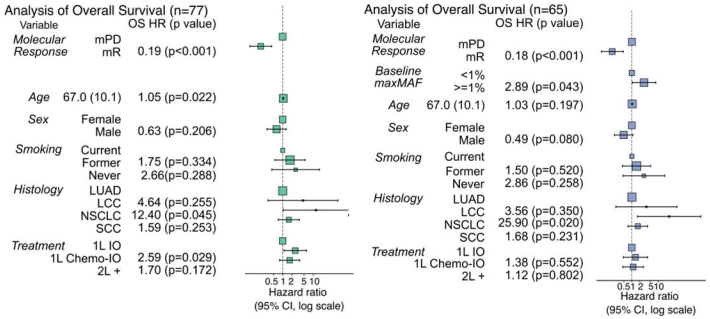

Fig.5. Independent prediction of overall survival for landmark molecular response.

Conclusions

Landmark ctDNA molecular response provides a real-time and accurate approach for monitoring immunotherapy clinical outcomes. Although not currently validated for regulatory use, assessing landmark ctDNA molecular response 3-9 weeks after ICI initiation provides potential for early interception of primary therapy resistance.

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