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GUARDANT360™

Use of comprehensive cell-free circulating tumor DNA analysis to identify genomic biomarkers in newly diagnosed advanced non-small cell lung cancer patients

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Introduction

- In advanced NSCLC patients, current guidelines recommend broad molecular profiling for EGFR, ALK, BRAF, and ROS1 and consideration of testing for other emerging targets such as, RET, MET, ERBB2, BRAF, and NTRK. Although KRAS is not actionable, it is informative due to its mutual exclusivity with other biomarkers [1,2].

- Comprehensive plasma-based genotyping may provide more complete assessment of all guideline-recommended biomarkers than tissue.

- The present study was conducted to prospectively assess performance of cfDNA compared to standard of care (SOC) tissue-based genomic testing to identify guideline recommended alterations in NSCLC patients.

Methods

- In this prospective, multicenter study, blood samples from treatment-naïve stage IIIB-IV NSCLC pts were tested using a well-validated comprehensive next-generation sequencing (NGS) cfDNA panel (Guardant360™) and compared with SOC tissue testing.

- The primary objective was to demonstrate the non-inferiority of cfDNA vs. tissue analysis for the detection of seven guideline-recommended biomarkers (not including KRAS) in NSCLC (10% non-inferiority margin based on Wald's method). [3]

- Secondary and exploratory analyses included response rates in the targeted therapy treatment group, tissue and cfDNA insufficiency rates and rate of biomarker-complete genotyping and estimation of positive predictive value (PPV) of cfDNA.

Results

Table 1.
Cohort characteristics (N=186).

- Between August 2016 - June 2017, 199 patients were enrolled and 186 were eligible for the final analysis.
- Thirteen patients (6.5%) were excluded based on the study inclusion and exclusion criteria.
- All patients were required to have tissue available at the time of diagnosis and a blood sample collected pre-treatment.
- The clinical and demographic characteristics of the 186 subjects are shown in Table 1.

Characteristics	Categories	(N=186)
Median Age (Range)	64 .3years (39 to 86)	
Gender, n (%)	Male Female	121 (65%) 65 (35%)
Race, n (%)	Caucasian Other	180 (97%) 6 (3%)
Histology, n (%)	Adenocarcinoma Other	172 (92%) 14 (8%)
Performance status, n (%)	0 1 2	45 (24%) 113 (61%) 28 (15%)
Smoking Hystory, n (%)	Never Former Current Unknown	51(27%) 60 (32%) 72 (39%) 3 (2%)
Prior chemotherapy (for early stage NSCLC), n (%)	Yes No	11 (6%) 175 (94%)

Figure 1.
Detection of actionable biomarkers characteristics.

The non-inferiority of cfDNA relative to SOC tissue testing was significantly demonstrated (p<0.05, CI -7.5% to +5.4%).

- cfDNA testing detected 46 (24.7%) patients with at least one of the 8 actionable biomarkers; tissue testing detected 48 (25.8%).
- Although KRAS was not included in the non-inferiority analysis, it is an informative biomarker given its mutual exclusivity with other actionable targets. Figure 1 shows detection rates by gene in cfDNA and tissue.

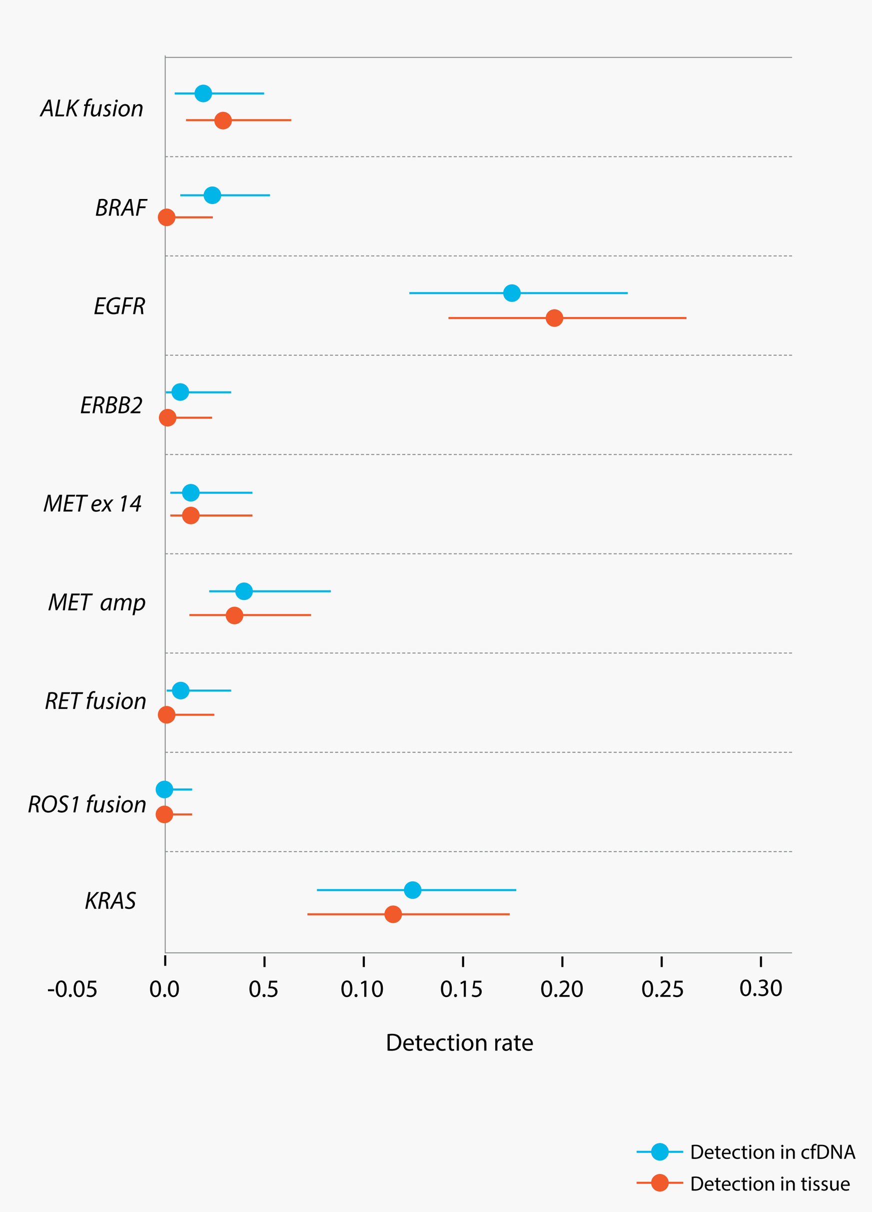
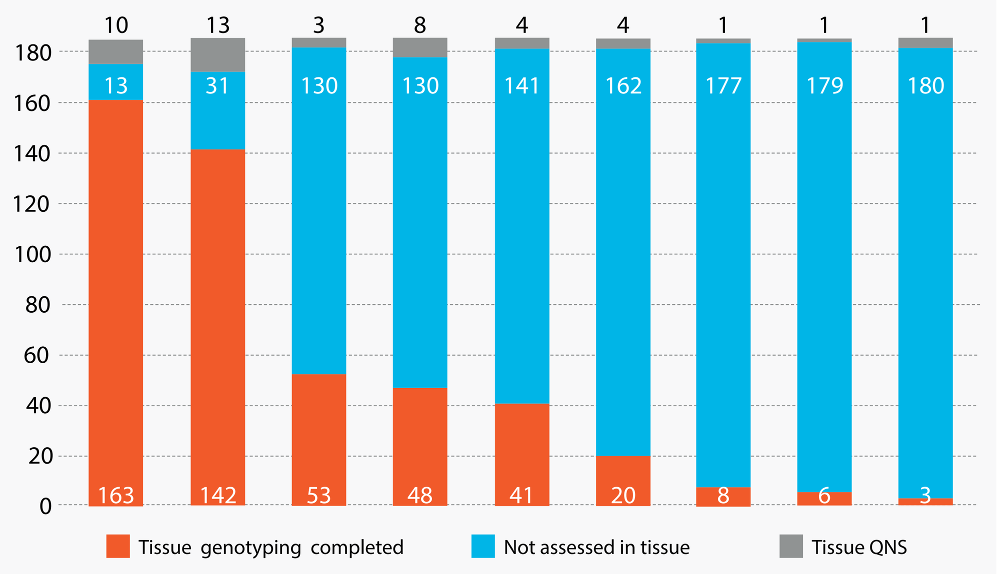


Figure 2.
Tissue Incompleteness, QNS and TND rates.

- Less than a third of patients had tissue-based testing for KRAS, ROS1, MET, BRAF and RET compared to 90.8% using cfDNA. Tissue genotyping rates for biomarkers other than EGFR and KRAS ranged from 1.6% to 28.5%.



*QNS was defined as samples negative for an actionable biomarker and not successfully genotyped for all genes.

Figure 3.
Informative biomarkers identification by tissue and cfDNA testing as primary genotyping.

- If tissue was the primary genotyping test, 57.1% of the 119 patients with an informative biomarker would have been identified, with an additional 42.9% of patients identified on reflex cfDNA testing. Using cfDNA genotyping as the primary genotyping test, 80.7% of the 119 patients with an informative biomarker would be identified with initial cfDNA testing, with the remaining 19.3% of patients identified with reflex tissue genotyping.

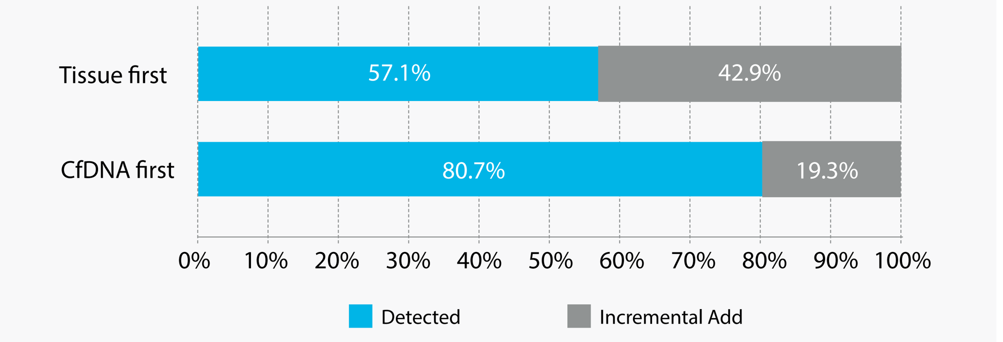
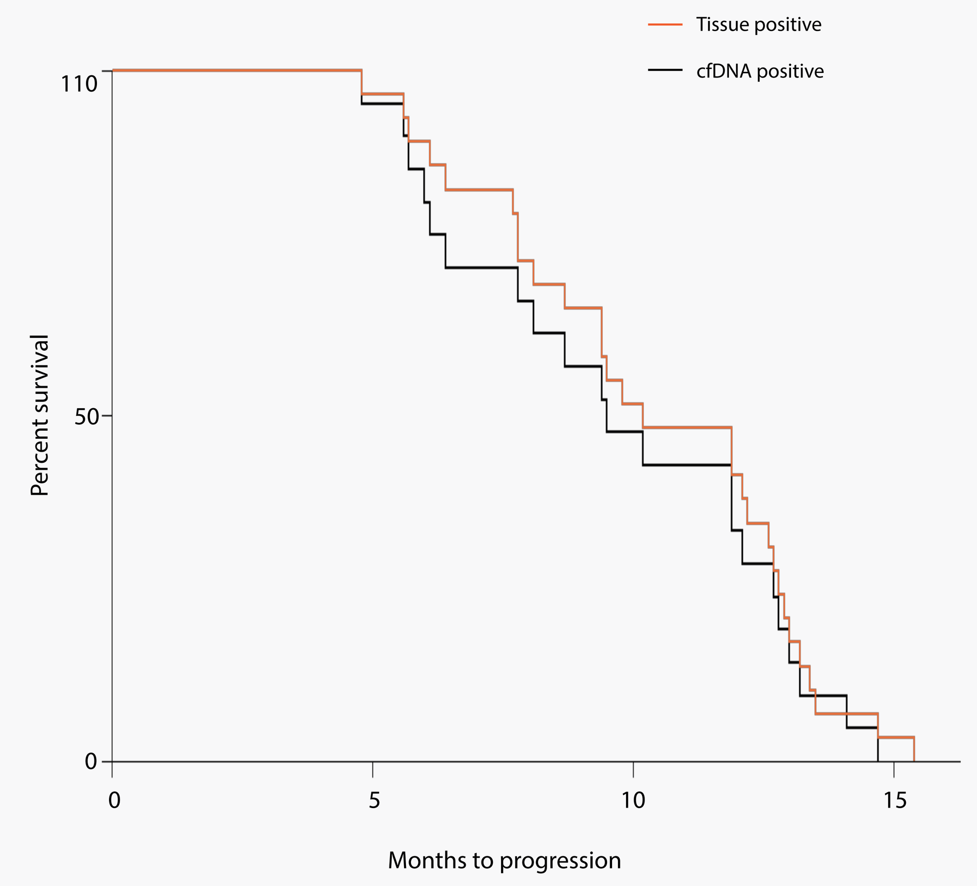


Figure 4.
Progression-free survival (PFS) in tissue and cfDNA positive cohorts.

The PPV of cfDNA was 100% (n=25/25^) for EGFR and 66.7% (2/3, 95%CI 17.7%, 94.9%) for ALK. Progression-free survival for the overall cohort of tissue and/or cfDNA positive patients treated with targeted therapy was 8.6 months (95%CI 7.6, 11.6).

- The PFS in the tissue positive cohort was 10.2 months and 9.5 months in the cfDNA positive cohort. These two cohorts had significant patient overlap, which precluded statistical analysis.
- Overall response rate in the patients treated with targeted therapy was 61.3% (95%CI 42.2%, 78.2%) based on blinded assessment, which is similar to previously reported targeted therapy response rates for first-generation EGFR and ALK inhibitors.



^ Includes one case that was tissue negative on initial genotyping but EGFR L858R positive on subsequent tissue testing

Conclusions

- This is the first prospective, multi-center study reporting outcomes and demonstrating that a comprehensive and highly sensitive cfDNA NGS assay is non-inferior to SOC tissue testing for the detection of guideline-recommended actionable genomic alterations in NSCLC.

- By modeling a blood-first approach to genotyping, comprehensive cfDNA testing identified 80.7% of the patients with informative biomarkers, while SOC tissue testing identified 57.1%. These results are confirmed in a parallel prospective, multicenter North American study [4].

- The PPV of the cfDNA assay utilized was high, supporting the use of cfDNA in treatment selection, which was confirmed with PFS and overall response rates similar to those previously reported.

- These results demonstrate the clinical utility of comprehensive cfDNA genotyping to identify targetable biomarkers in newly diagnosed advanced NSCLC patients.

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