Cell-Free DNA (cfDNA) testing in lung adenocarcinoma (LUAC) patients: Spanish Lung Liquid versus Invasive Biopsy Program (SLLIP)

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Background

- Liquid biopsies are a revolution in cancer diagnostics as a minimally invasive alternative to tissue biopsy[1].
- cfDNA is used for the detection of biomarkers in advanced LUAC patients if a tumor tissue sample is infeasible, i.e. tissue quantity not sufficient, tissue unobtainable, or tissue biopsy analysis cannot be completed within two weeks [2,3].
- Genotyping of 7 specific genes is recommended in LUAC patients [4,5] as use of targeted therapy significantly improves response rates vs. use of chemo- and/or immuno-therapy.
- However, no study has examined whether a liquid biopsy can identify recommended genomic targets as efficiently as standard of care tissue-based genomic testing.
- The SLLIP study (clinicaltrials.gov registration NCT03248089) prospectively evaluated a well-validated cfDNA NGS assay (Guardant360™) compared to standard of care tissue-based genomic testing for the detection of actionable genomic targets in untreated metastatic LUAC.

Methods and Design

Study design

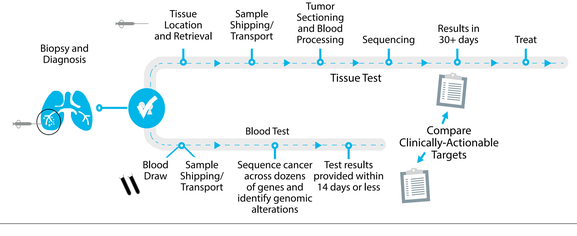
- Prospective, multicenter study of consecutively tested metastatic non-squamous NSCLC patients with no prior treatment for advanced disease, age ≥18, and ECOG PS 0-2
- Tumor tissue was genotyped according to local practice, and compared to results from a plasma-based comprehensive genomic profiling test, Guardant360® (Guardant Health, Inc., Redwood City, CA, USA) at the time of enrollment.
- Guardant360 is a 68-73-gene plasma-based comprehensive genomic test that includes all NCCN guideline-recommended genomic targets and all four major classes of genomic alterations. This cfDNA NGS assay uses DNA hybrid capture and digital barcoding to assure ultra-high specificity while achieving high sensitivity (95% limit of detection to 0.25% for SNVs, 0.2% for indels and fusions, and amplifications to 2.24 plasma copy number) with reportable ranges down to 0.04%, 0.01%, 0.04% variant allele fractions, and 2.12 plasma copy number, respectively.
- Enrollment of at least 182 subjects was planned to have at least 165 eligible.
- Study schema is outlined in **Figure 1.**

Study Objectives

Primary objectives:

- Demonstrate non-inferiority of cfDNA vs. standard of care tissue testing for the detection of actionable biomarkers. Actionable biomarkers were defined as alterations in EGFR, ALK, ROS1, BRAF, ERBB2, MET, and RET (6). Subjects with at least one actionable mutation were defined as positive.
- Secondary objectives:
- Tissue incomplete (TI) rate for tissue testing (proportion of subjects whose tumors did not have an actionable biomarker and were not tested for actionable biomarkers in all 7 genes).
- Quantity Not Sufficient (QNS) rate for tissue and Tumor Not Detected (TND) rate (no alterations detected) for cfDNA.
- Turnaround time (TAT) for biomarker results (tissue and cfDNA) measured from date of order to date of result (includes time to tissue/blood acquisition and shipping after ordering).

Figure 1.



Study sponsor responsible for data collection and analysis: Medica Scientia Innovation Research-MEDSIR; Funding source: Guardant Health, Inc.

Results

Characteristics of enrolled cohort

Table 1. Cohort characteristcs (N=185)

Median Age		64 years (39 to 86)
Gender	Male	64 (35%)
	Female	121 (65%)
Race	Caucasian	179 (97%)
	Other	6 /3%)
Histology	Adenocarcinoma	171 (92%)
	Other	12 (8%)
Performance status	0	44 (24%)
	1	113 (61%)
	2	28 (15%)
Smoking Hystory	Never	50 (27%)
	Former	65 (35%)
	Current	67 (36%)
	Unknown	3 (2%)
Prior chemotherapy (for early stage NSCLC)	Yes	11 (6%)
	No	174 (94%)

Table 1. Between August 2016 to July 2017. 199 patients were enrolled at 10 sites in Spain, with 185 found eligible.

Reasons for ineligibility were as follows:

- concurrent other malignancy (n=5),
- blood sample not provided (n=5),
- received exclusionary therapy prior to enrollment (n=1),
- metastatic diagnosis not confirmed at time of enrollment (n=1),
- tissue genotyping not ordered (n=1), other lung cancer diagnosis (squamous cell carcinoma, n=1).

Detection of actionable biomarkers

Standard of care tissue testing detected 48 patients with actionable biomarkers; cfDNA testing detected 47. The non-inferiority* of cfDNA, relative to standard of care tissue testing, was significantly demonstrated (p<0.002). The 95% confidence interval for the difference in detection rates is -6.9 % to +5.8%.

Figure 2A. Detection rates for actionable biomarkers in cfDNA vs. tissue.

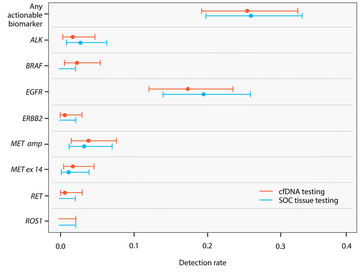
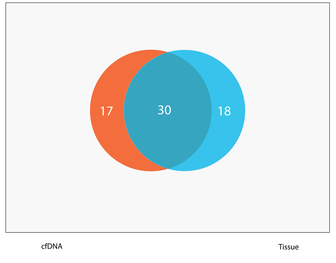


Figure 2B. Subjects identified as positive for actionable biomarkers by cfDNA and tissue.



*The non-inferiority margin was 10%. Non-inferiority was demonstrated by the adjusted Wald confidence interval[7]. The nominal α level was 0.025.

Tissue Incompleteness, QNS and TND rates

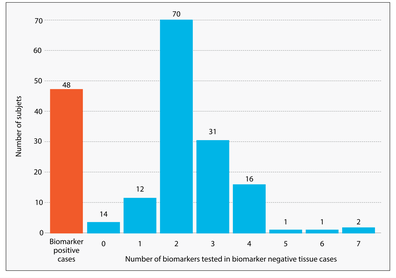


Figure 3.

- 135/185 (73%) of patients enrolled were biomarker negative and had incomplete genotyping for all 7 actionable biomarkers. The majority of biomarker negative patients had tissue genotyping for 2 biomarkers (most commonly EGFR and ALK).
- QNS (tissue) vs. TND (blood) rates (data not shown)
  - 25 (13.5%) subjects were both: Tissue negative for any actionable biomarker, and QNS for at least one actionable biomarker tested.
  - 17(9.2%) subjects were reported by the Guardant360™ assay as TND.

Turnaround time

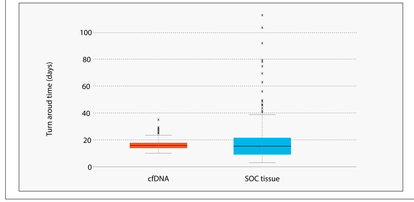


Figure 4.

- The median TAT for cfDNA testing was 14 days. This was not a statistically significantly difference (p=0.191).

Conclusions

- Advanced LUAC patients are often under-genotyped for guideline-recommended targetable alterations.
- The SLLIP study demonstrates that a comprehensive and highly sensitive cfDNA NGS assay, when compared to SOC tissue-based genomic testing. is non-inferior at detecting recommended targetable somatic genomic alterations in LUAC patients.
- Lack of sufficient tissue and incomplete tissue genotyping can be mitigated by the use of plasma-based comprehensive genomic testing.

References

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