Abstract #9019

LIBELULE: a randomized phase III study to evaluate the clinical relevance of early liquid biopsy in patients with suspicious metastatic lung cancer

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OBJECTIVES

First "real-life" randomized study to evaluate the feasibility and clinical relevance of early liquid biopsy (LB) to shorten Time to Treatment Initiation (TTI), in frontline setting of advanced lung cancer

CONCLUSIONS

- **Early LB significantly reduces the time to initiation of an appropriate 1st-line therapy in patients eligible for systemic treatment, especially for those with actionable alterations indicating targeted 1st-line therapy**
- **Early LB significantly reduces the time to a contributive molecular analysis by an average of 8 days**
- **Performing a liquid biopsy as early as possible for suspected advanced lung cancer helps to obtain a genomic profile and accelerates the initiation of appropriate treatment**
- **Further analyses will include progression-free survival, quality of life analyses, cost-effectiveness and budget impact analyses**

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BACKGROUND

Genomic testing is a major component of the therapeutic decision in 1st-line treatment of advanced NSCLC. Timeliness of biomarker testing is essential to minimize the time to treatment initiation (TTI) or avoid inappropriate treatment. We hypothesized that early liquid biopsy (LB)-based molecular testing performed at the patient's first visit could reduce this TTI.

METHODS

LIBELULE is a multicenter, randomized, comparative, open-label study, enrolling pts with radiological suspicion of stage IV lung cancer, and no prior biopsy or cytology for advanced NSCLC diagnosis.

DESIGN (Figure 1)

- **Arm A (experimental arm): LB performed at the 1st visit. We identified 3 situations:**
  - ✓ *Category 1 alterations* with targeted therapies available in 1st line (*EGFR*-, *BRAF* V600E mutation, *ALK*- or *ROS1*-rearrangement) identified on LB → LB results only were sufficient to initiate targeted treatment
  - ✓ *Category 2 alterations* without targeted therapies available in 1st line (*ERBB2*, *MET* exon 14, *KRAS*, *BRAF* non V600 and/or *LKB1* mutation, *RET*- or *NTRK*-rearrangement) identified on LB → LB **and** pathological report (including PD-L1) were mandatory to initiate treatment
  - ✓ *Other or no molecular alterations* detected on LB → LB **and** pathological report **and** molecular report on tissue were mandatory to initiate treatment
- **Arm B (control arm): histological sampling was planned with genomic analysis when indicated (local LB allowed)**

LB: InVisionFirst®-Lung assay is an amplicon-based NGS panel covering 37-NSCLC associated genes, including SNVs, CNVs, indels and fusions (Figure 2.).

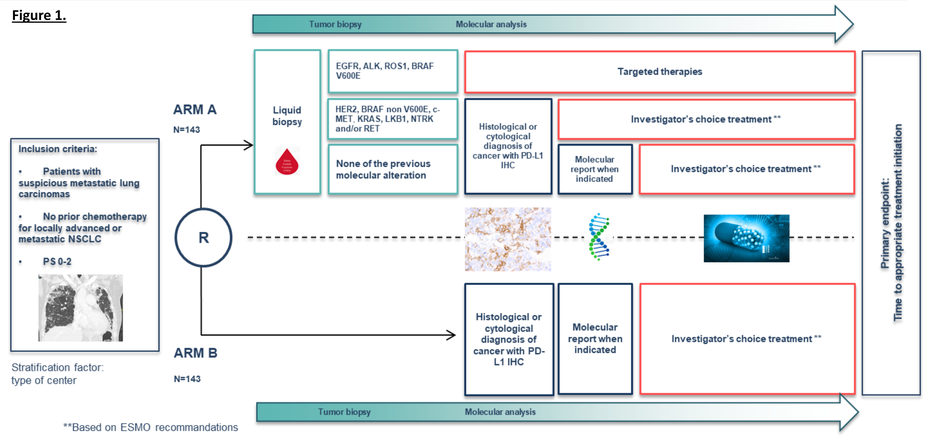
Figure 2.

SAMPLE SIZE

Based on a French retrospective study on ~250 advanced NSCLC patients, the mean TTI was 42 days (associated standard deviation: 22.5 days)[1].
The expected decrease of the mean TTI in the experimental group is based on the following hypotheses:
- a 21 days diminution in the category 1 alterations (expected to represent 13% of the population[2])
- a 17 days diminution in the category 2 (expected to represent 36% of the population[2])

It results in a mean TTI in the experimental group of 33 days (21% reduction of TTI). The sample size calculation is based on a non-parametric 2-sided Wilcoxon Mann and Whitney test. Assuming a type I error alpha of 5% and 90% power, 286 patients are needed to reject the null hypothesis H0: the TTI distributions are not different between experimental and control groups.

Figure 1.



ENDPOINTS

- **The primary endpoint** was the time from randomization to initiation of appropriate treatment based on informative genomic and pathological results.
- Secondary endpoints were time to availability of informative molecular pathology results, rate of treatment initiated before obtaining molecular results, progression-free survival, safety of diagnosis procedures, quality of life, anxiety and depression level, the concordance between the molecular status on tissue and liquid biopsies, the rebiopsy avoidance rate for molecular status determination with the use of liquid biopsy, cost-effectiveness and budget impact analyses.

RESULTS

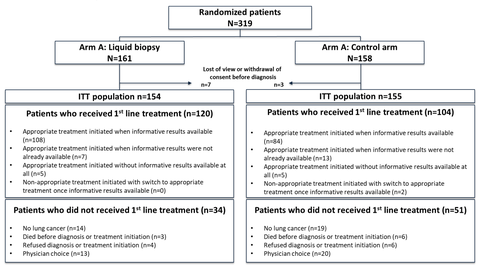
- 319 pts were randomized between Arm A (n=161) and B (n=158): median age was 68 years (39-97), 56.1% were male, 28.5% were non-smokers, 18.1% were PS≥2. Histologies were distributed as follow: adenocarcinoma (56.7%), squamous cell carcinoma (11%), SCLC (10%), other tumor types (5%). 5.3% of patients were found to be cancer-free at the end of the workup.

Baseline patients' characteristics

		Arm A Liquid Biopsy N=161	Arm B Control N=158
Median age, years (range)		68 (39-97)	68 (43-94)
Sex female, n(%)		65 (40.4%)	75 (47.5%)
Smoking history			
	Never	49(30.4%)	42 (26.6%)
	Current	40 (24.8%)	40 (25.3%)
	Former	72 (44.7%)	76 (48.1%)
Histology, N (%)			
SCLC		14 (8.7%)	18 (11.4%)
NSCLC		121 (75.2%)	113 (71.5%)
	Adenocarcinoma	94 (58.4%)	87 (55.1%)
	Squamous	18 (11.7%)	17 (10.8%)
	Other	9 (5.6%)	9 (5.7%)
No lung cancer		14 (8.7%)	19 (12%)
No cancer		9 (5.6%)	8 (5.1%)
No diagnosis obtained		12 (7.5%)	8 (5.1%)
PS			
	0	46 (28.6%)	50 (31.6%)
	1	84 (52.2%)	78 (49.4%)
	≥2	29 (18%)	28 (17.7%)
	Missing	2 (1.2%)	2 (1.3%)

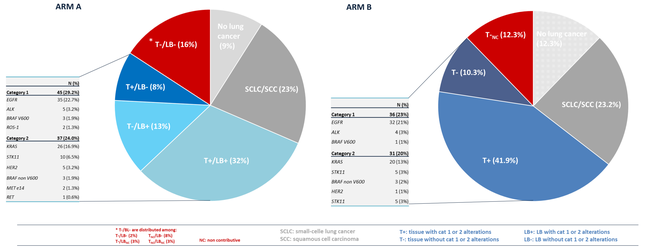
Treatment initiation in each arm

- Systemic treatment was initiated in 74.5% and 65.8% of patients in Arm A and B, respectively. Main reasons for not initiating treatment were diagnosis other than cancer, local treatment and palliative care.



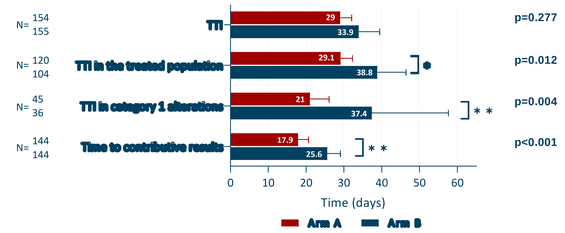
Patients' molecular profile

- In Arm A, 81% of patients had ctDNA findings.
  - ✓ **Turn-around time for LB analysis was 6 days** (9 days including shipment to the US).
  - ✓ Category 1 and category 2 alterations were identified on tissue and/or LB in 29.2% and 24%, respectively. *EGFR* mutations were found in 21.7% of patients.
- In Arm B, 23.2% of patients had category 1 and 20% had category 2 alterations detected. *EGFR* mutations were found in 20.3% of patients.



Time to treatment initiation

- If no systemic lung therapy was initiated, TTI used the physician decision (surveillance, local therapy), death or patient refusal date.
- The mean TTI was 29.0 days (95%CI 25.9-32.1) in Arm A versus 33.9 days (95%CI 28.4-39.5) in Arm B in the intention-to-treat population.
- The mean TTI was **9.7 days shorter** in Arm A for **patients who received systemic treatment.**
- It was also **16.4 days shorter in patients with category 1 alterations**.
- **The time to contributive genomic analysis was also reduced by 7.7 days**.



Representation of time to contributive genomic profile in patients with category 1 and 2 alterations

- In Arm A,
  - ✓ In patients with category 1 alterations (left graph), treatment could have theoretically been initiated at the time of liquid biopsy report reception (red dots). As shown by the red bars and blue dots, some physicians tend to wait for the molecular report on tissue to initiate treatment, which tends to increase the TTI.
  - ✓ In patients with category 2 alterations (right graph), pathological results (grey stars) were obtained 4.9 days (-9.0-36.0) after liquid biopsy results (red dots), which could allow to initiate faster an appropriate treatment based on informative results.
- In both arms, **mean time between informative results and treatment initiation was 12.9 days** (0-346) similar between category 1 (14 days (0-346)) and 2 (12.4 days (0-61)) alterations patients'. 29,1% of patients initiated treatment ≥15 days following reception of informative results including 10.8% in more than 30 days.
- In Arm A, **7.4% of patients versus 13.3% in Arm B initiated a treatment without genomic analysis available**.

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