BACKGROUND

Genomic testing is a major component of the therapeutic armamentarium 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

LIBELLE 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 disease.

DESIGN (Figure 1)

- Arm A (experimental arm): LB performed at the 1st visit. We studied 3 situations:
  - Category 1 alterations: with targeted therapy 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, ALK, BRAF v600E and/or MET-rearrangement, RET- or NTRK6 rearrangement) identified on LB and pathologic report (including PD-L1) were mandatory to initiate treatment
  - Other or no molecular alterations detected on LB: LB and pathologic report on tissue were mandatory to initiate treatment
- Arm B (control arm): histological sampling was planned with genetic analysis when indicated (local lab allowed)

In addition, LB was implemented in an amplicon-based NSG panel covering 37 NSCLC associated genes, including SMARCA, CNVs, indels and fusions (Figure 2).

RESULTS

- 134 pts were randomized between Arm A (n=67) and B (n=67): median age was 68 years (range 39-77), 56% were male, 20% were non-smokers, 16% were PS Zubko. Histologies were distributed as follows: adenocarcinoma (36%), squamous cell carcinoma (21%), SCC (10%), other tumor types (5%). 53% of patients were found to be cancer-free at the end of the study.

<table>
<thead>
<tr>
<th>Baseline patients’ characteristics</th>
<th>Arm A</th>
<th>Arm B</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (stdev)</td>
<td>67 (11)</td>
<td>68 (10)</td>
<td>0.65</td>
</tr>
<tr>
<td>Sex</td>
<td>29 (44%)</td>
<td>29 (44%)</td>
<td>1</td>
</tr>
<tr>
<td>Non-smoker</td>
<td>31 (46%)</td>
<td>31 (46%)</td>
<td>1</td>
</tr>
<tr>
<td>PS 0</td>
<td>23 (34%)</td>
<td>22 (33%)</td>
<td>0.71</td>
</tr>
<tr>
<td>Histology</td>
<td>23 (34%)</td>
<td>23 (34%)</td>
<td>1</td>
</tr>
<tr>
<td>EGFR wild</td>
<td>40 (60%)</td>
<td>37 (55%)</td>
<td>0.41</td>
</tr>
<tr>
<td>EGFR mutant</td>
<td>27 (40%)</td>
<td>30 (45%)</td>
<td>0.37</td>
</tr>
<tr>
<td>Architectural classification</td>
<td>40 (60%)</td>
<td>37 (55%)</td>
<td>0.41</td>
</tr>
</tbody>
</table>

P-values were calculated using a parametric t-test.

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 on 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 treatments

- Further analyses will include progression-free survival, quality of life analyses, cost-effectiveness and budget impact analyses

REFERENCES


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 initiation 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 necropsy avoidance rate for molecular status determination with the use of liquid biopsy, cost-effectiveness and budget impact analyses.

- The contributive hypothesis 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) a 17 days diminution in the category 2 alterations (expected to represent 38% of the population) a 23 days diminution in the experimental group of 31 days (15% 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. The TTT diminution are not different between experimental and control groups.

- The mean TTT in the experimental group is 31 days (15% 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. The TTT diminution are not different between experimental and control groups.

- Further analyses will include progression-free survival, quality of life analyses, cost-effectiveness and budget impact analyses.

- The time to contributive genomic analysis was also reduced by 7.6 days.

- The contributive hypothesis has been validated with a p<0.001.

- In Arm A, 83% of patients had CRAD findings.

- Turn-around time for LB analysis was 6 days (95% including shipment to the CRL.

- Contributed as follow: following up the requirements of the CRL. 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. The TTT diminution are not different between experimental and control groups.

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- In Arm A, patients with category 1 alterations left (graph), treatment could have theoretically been initiated at the time of liquid biopsy result reception (red dots). As shown by the red bars and blue dots, some physicians tend to wait for the molecular result on tissue to initiate treatment, which leads to a treatment delay.

- In Arm A, patients with category 2 alterations (right graph); pathological results (gray stars) were obtained 4.6 days (9.3-0.5) after liquid biopsy result (red dots), which could be awaited to foster an appropriate treatment based on informative results.

- In both arms, mean time between informative results and treatment initiation was 12.9 days (9.4-16) similar between category 1 and 2 alterations.

- In Arm A, 23.2% of patients had category 1 and 20% had category 2 alterations detected. EGFR mutations were found in 20.3% of patients.

- In Arm B, patients with category 1 alterations left (graph), treatment could have theoretically been initiated at the time of liquid biopsy result reception (red dots). As shown by the red bars and blue dots, some physicians tend to wait for the molecular result on tissue to initiate treatment, which leads to a treatment delay.

- In Arm A, 7.4% of patients versus 13.3% in Arm B initiated a treatment without genomic analysis available.