Genomic Characterization of First-line Advanced or Metastatic Non-small Cell Lung Cancer Patients Subgroups Associated with Good/Bad Prognosis

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BACKGROUND

The development of new therapies has significantly improved survival rates in patients with advanced or metastatic non-small cell lung cancer (aNSCLC)1. However, certain subgroups of patients either do not benefit or benefit significantly more from these treatments, and little evidence is available on why these patients respond differently.

We aimed to identify any association between non-driver mutational patterns and four subgroups of patients of special interest.

METHODS

This retrospective cohort study analysed the nationwide (US-based) de-identified Flatiron Health Foundation Medicine aNSCLC clinic-genomic database (FH-FMI CGDB). Data were sourced from approximately 280 US cancer clinics (~800 care facilities), extracted from EHR data, curated via technology-enabled abstraction, and linked to genomic data derived from FMI tests in the FH-FMI CGDB by de-identified, deterministic matching.

We selected aNSCLC patients who had initiated first-line (1L) cancer immunotherapy (CT), alone or in combination, or chemotherapy in routine clinical practice between 2016 and 2021. Multivariate logistic regression models adjusted for key covariates were used to evaluate the presence of non-driver mutations in four subgroups described in the literature: fast progressors (median progression-free survival [mPFS] <3 months), long-term survivors (mPFS >12 months), females, and never-smokers.

RESULTS

- In total, 10,795 patients were selected and 2,999 met the inclusion criteria (Figure 1). aNSCLC CGDB September 30, 2021 data cut

<table>
<thead>
<tr>
<th>Mutation</th>
<th>All treatments combined</th>
<th>Chemotherapy</th>
<th>CIT-combining</th>
</tr>
</thead>
<tbody>
<tr>
<td>STK11</td>
<td>OR [95% CI]</td>
<td>p-value</td>
<td>matched subtypes</td>
</tr>
<tr>
<td>Non-FP</td>
<td>254/1385</td>
<td>0.015</td>
<td>0.50 [0.31-0.80]</td>
</tr>
<tr>
<td>FP</td>
<td>1.01 [1.00-1.01]</td>
<td>0.001</td>
<td>0.58 [0.37-0.90]</td>
</tr>
<tr>
<td>Non-LTS</td>
<td>326/1230</td>
<td>0.000</td>
<td>0.01 [0.00-0.04]</td>
</tr>
<tr>
<td>LTS</td>
<td>0.99 [0.98-1.01]</td>
<td>0.001</td>
<td>0.99 [0.98-1.01]</td>
</tr>
<tr>
<td>Female</td>
<td>832/2228</td>
<td>0.000</td>
<td>0.48 [0.37-0.62]</td>
</tr>
<tr>
<td>Never-smoker</td>
<td>316/676</td>
<td>0.000</td>
<td>0.55 [0.43-0.71]</td>
</tr>
</tbody>
</table>

Table 1. Prevalence of selected non-driver mutations in the overall study population and by treatment group.

- Fast progressors were characterized by a significantly higher prevalence of STK11, KEAP1, and CDKN2A/B mutations compared to non-fast progressors (odds ratio [OR] >1) (Table 1).
- Long-term survivors showed a significantly lower prevalence of STK11, KEAP1, CDKN2A/B (1), and FGFR mutations (OR <1), and a higher prevalence of KRAS mutations (OR >1).
- Women were less likely to harbour mutations in APC (OR 0.53) and FGFR (OR 0.58), while KRAS mutations were more frequent in this population (OR 1.98).
- In never-smokers, STK11 and KEAP1 mutations were significantly less prevalent (OR <1) (Table 1). In addition, this subgroup also showed a trend towards a lower prevalence of FGFR and higher prevalence of HRAS.
- When analysing these subgroups by treatment, a trend emerged among KRAS-mutated patients, suggesting a larger proportion of long-term survivors in the group that received CIT (20%), alone or in combination, compared to chemotherapy alone (14%). However, these differences did not reach statistical significance (p = 0.23).

CONCLUSIONS

- STK11, KEAP1, and CDKN2A/B mutations were significantly associated with fast progression.
- STK11, KEAP1, CDKN2A/B, and FGFR mutations were significantly associated with shorter survival. Women were less likely to harbour these mutations, while a higher prevalence was detected in smokers.
- Our results may assist in identifying aNSCLC patients who will respond better or worse to treatment, either with immunotherapy or chemotherapy.

References: 1. Rodon G, et al. (2021). 2. Cittone of interest: Mariano Provencio has received consulting/advisory and/or speaker honorarium from Roche, Merck, Meril, AstraZeneca, Lilly, Pfizer, Bayer, Angen, Jenson, GSK, Teva, and Small, and research grants from Roche and Merck. Funding: This study was funded by Roche. Acknowledgements: The authors would like to thank Dr. Victor Lalone and Dr. Javier Arribas-Nicolás, of Medical Statistics Consulting, for medical writing services.