Squamous cell carcinoma accounts for ~25% of non-small-cell lung cancer (sq-NSCLC) and compared to lung adenocarcinoma has a distinct molecular landscape\(^\text{1}\). Smoking is a major risk factor for and influences the molecular landscape of sq-NSCLC\(^\text{2}\). Comprehensive molecular profiling to identify genomic driver/actionable mutations is inconsistently performed for sq-NSCLC. Clarifying the molecular and immune landscapes of sq-NSCLC by smoking status will help guide therapeutic decision making.

Methods

2413 sq-NSCLC tumors with smoking history (obtained from medical records) were analyzed using Next Generation Sequencing (NGS, 592 gene panel, NextSeq), Whole Exome or Whole Transcriptome Sequencing (WES, WTS, NovaSeq), and IHC at Cars Life Sciences (Phoenix, AZ). Further, 130/2413 tumors had both DNA (NGS-592/WS) and RNA (WTS) sequencing data.

Based on their smoking history, patients were categorized as nonsmokers (never-smokers) and smokers (ever-smokers).

For the prevalence tables, ‘Fusion’ and ‘Transcriptome’ incorporate technologies capturing fusion events, ‘NGS’ captures gene mutations, while ‘CNA’ accounts for copy number amplified events.

Immune cell estimates were calculated using microenvironment cell population (MCP) counter analysis. Significance was determined using chi-square, Fisher-Exact or Mann-Whitney U and p-adjusted for multiple comparisons (q < 0.05 or FDR<0.25) where applicable.

Results

Table 1: Cohort characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Nonsmokers (n=66)</th>
<th>Smokers (n=2347)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age (range)</td>
<td>69.0 (37-89)</td>
<td>70.0 (32-89)</td>
</tr>
<tr>
<td>Male (% prevalence)</td>
<td>60.60%</td>
<td>62.00%</td>
</tr>
<tr>
<td>Female (% prevalence)</td>
<td>39.40%</td>
<td>38.00%</td>
</tr>
</tbody>
</table>

Table 2: Molecular landscape associated with smoking history. Alterations in TPS, RB1 and CDKN2A were more prevalent among smokers, while SETD2 and BAP1 mutations were more prevalent in nonsmokers. In the "A percentage" column, darker shades indicate higher prevalence of gene alteration in that cohort. In the "Δ percentage" column, orange bars indicate enrichment of alterations in smokers vs nonsmokers while blue bars indicate the opposite. *p<0.05, q<0.05; *p=0.05 & q<0.05.

Table 3: Alterations in driver/actionable (D/A) target genes among smokers and nonsmokers. When focusing on D/A target genes, mutations in EGFR and MET identified in smokers were significantly associated with higher prevalence of gene alteration in that cohort. *indicates p<0.05, q>0.05 while *indicates p<0.05 and q<0.05.

Table 4: GSEA in Smokers vs Nonsmokers. Median TMB was significantly higher in smokers compared to nonsmokers. *indicates pathway significantly enriched in smokers compared to nonsmokers.

Table 5: PD-L1 expression break down among Smokers and Nonsmokers. There were no statistically significant differences in PD-L1 expression among smokers and nonsmokers regardless of the PD-L1 expression-based grouping.

Table 6: MSS and TMB status in Smokers vs Nonsmokers. A similar trend in reduction was observed in PD-L1*. *indicates p<0.05, q<0.05 while *indicates p<0.05 and q<0.05.

Conclusions

• Actionable alterations in target genes such as EGFR and MET were more prevalent in nonsmokers while those in KRAS were more prevalent in smokers. GSEA revealed an enrichment of the JAK-STAT signaling pathway in nonsmokers compared to smokers.
• Median TMB was significantly higher in smokers compared to nonsmokers. Expression of immune checkpoints CD80, CD86, TIM-3 and PD-L2 were significantly increased in nonsmokers compared to smokers.
• Immune cell infiltrates including NK cells, macrophages and MDCs were significantly associated with higher prevalence of immune checkpoint 

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References