1083P-The analysis Molecular characteristics, PD-L1, TMB and MSI in Chinese NF1-mutated NSCLC

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**BACKGROUND**

- The tumor suppressor gene neurofibromin 1 (NF1) is a major regulator of the RAS-MAPK pathway and NF1 mutations have been reported in various cancers including non–small-cell lung cancer (NSCLC). NF1 mutations define a unique population of NSCLC.
- But best treatment patterns in the NF1 mutation group is unclear . Herein, we assessed the molecular characteristics, tumor mutational burden(TMB), microsatellite instability(MSI) and PD-L1 expression in Chinese NF1-mutated NSCLC to explore the possibility of Immunotherapy.

**METHODS**

- In this study, we retrospectively analyzed NF1 mutations, TMB and MSI using next-generation sequencing(NGS), PD-L1 status was determined by VENTANA PD-L1 (SP263) Assay. For the purposes of this study, we only analyzed loss-of-function (LOF) and predicted loss of function mutations(PLOF) in the NF1 gene.

**RESULTS**

- A total of 202 LOF/PLOF NF1 mutations were found, and 28 patients carried double NF1- LOF/PLOF mutations. 183 unique NF1 nucleotide LOF/PLOF variants were identified in 174 patients.
- LOF/PLOF variants in NF1 included nonsense mutations (n=90), frameshift mutations (n=61), splice site mutations (n=42), and missense mutations (n=9). Mutations are spread throughout all exons of the NF1 gene.
- 56 NF1 variants identified in 52 tumors occurred with other driver mutations/fusions (EGFR (22); KRAS (19); MET(5); ROS1 (3); ALK(2); EGFR&KRAS(1);BRAF(0);ERBB2(0); RET(0)).
- The median TMB was significantly higher in patients harboring LOF/PLOF NF1 mutations compared with their wild-type counterparts. (8.1 vs.2.2, P <.001). No cases had an MSI-H status in the LOF/PLOF NF1 mutation cohort. 51 patients in the LOF/PLOF NF1 mutations cohort and 1326 patients in the wild-type NF1 cohort could be evaluated for PD-L1 tumor cell expression. PD-L1 tumor cell expression in the LOF/PLOF NF1 mutations cohort was significantly higher than in the wild-type NF1 cohort. (P <.001).

**Fig. 1.** LOF/PLOF Mutation Distribution in NF1

- Table 1. PD-L1, TMB, MSI in LOF/PLOF NF1 mutation cohort when compared to wild-type NF1 cohort

**CONCLUSIONS**

- The prevalence of LOF/PLOF NF1 mutations was 2.2% (174/7632) in Chinese NSCLC patients. LOF/PLOF NF1 mutations (29.9%) do exist with concurrent oncogenic alterations but the majority of LOF/PLOF NF1 mutations (70.1%) in NSCLC occur independently.
- NF1 mutation was associated with higher TMB and higher PD-L1 tumor cell expression. Immune Checkpoint Inhibitors may be considered as an option for patients with NSCLC harboring NF1 mutations.

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<table>
<thead>
<tr>
<th>Parameters</th>
<th>LOF/PLOF NF1 mutation cohort</th>
<th>wild-type NF1 cohort</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-L1 IHC</td>
<td>15%</td>
<td>25%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BRAF mutation (C/T=150)</td>
<td>3 (3)</td>
<td>10/120 (5%)</td>
<td></td>
</tr>
<tr>
<td>MET mutation (C/T=609)</td>
<td>15%</td>
<td>11%</td>
<td></td>
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<tr>
<td>TMB</td>
<td>91 (214)</td>
<td>50 (118)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mutation count(MSI)</td>
<td>24%</td>
<td>34%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 1. PD-L1, TMB, MSI in LOF/PLOF NF1 mutation cohort when compared to wild-type NF1 cohort