DNA Damage Response and Repair (DDR) Gene Mutations as an alternative mechanism to generate high TMB in never smokers NSCLC patients

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BACKGROUND

- Immune checkpoint inhibitors (IO) single agent or in combination with platinum-based chemotherapy (CT-IO) are standard of care for Stage IV and not oncogene addicted non-small cell lung cancer (aNSCLC) according to PD-L1 expression.
- The presence of a high tumor mutation burden (H-TMB) is one of the most debated biomarkers for IO response.
- Smoking-induced harm is a mechanism that generates an H-TMB in aNSCLC smoking patients (S-pts), whereas never-smoking patients (NS-pts) usually have a low TMB and are unresponsive to IO.
- However, the subgroup of NS-pts with an H-TMB has not yet been well characterized molecularly.

METHODS

- We retrospectively collected clinical data from a single-center cohort of 142 aNSCLC pts with PD-L1 ≥ 50% treated with first line pembrolizumab between January 2017 to March 2021.
- Next-generation sequencing (NGS) analysis using the FoundationOne®CDx assay (Foundation Medicine, Cambridge, MA, USA) was performed to correlate genetic alterations with clinical characteristics and response outcomes.
- We classified all detected mutations into eleven main pathways:
  - cell cycle
  - Hippo
  - Myc
  - Notch
  - Oxidative stress/Nrf2
  - PI3K
  - RTK/RAS/MAP
  - TGF beta
  - p53
  - beta-catenin/Wnt
  - DNA Damage Response Repair (DDR)

- Lastly, we identified the pathways with at least one mutation for each patient and performed enrichment analysis to characterize patients’ subgroups in terms of mutated pathways.

RESULTS

- Overall, with a median follow-up of 22 months (m), mPFS was 9.9m, and mOS was 10.6 m.
- There were 111 S-pts and 31 NS-pts. The cohort of S-pts had higher TMB than the NS-pts cohort (TMB average 10.05 vs. 8.86 Mut/Mb) (Figure 1).
- However, a subgroup of 11 NS-pts with high TMB (39-11 Mut/Mb) was identified. This subgroup was particularly enriched in DDR pathway mutations (p-value=0.0016) compared to the rest of the series and the H-TMB/S-pts subgroup (Table 1).
- All H-TMB/NS-pts responded to IO treatment with an mPFS of 10.9 m and mOS of 12.7 m.

CONCLUSIONS

Our data suggest a potential role of DDR signatures as an alternative mechanism to generate H-TMB in NS-pts. This preliminary observation could identify a subgroup of NS-pts responsive to IO and with a better prognosis.

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Figure 1. Overall population, violin plot TMB according to smoking status.

Table 1. hTMB population, pathway enrichment analysis by smoking status.

<table>
<thead>
<tr>
<th>Pathway</th>
<th>hTMB Yes (42 patients)</th>
<th>hTMB No (11 patients)</th>
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| Cell Cycle Pathway             | 0.9033                 | 0.2803                 | 8
| Hippo Pathway                  | 1                      | 0.2075                 | 1
| Myc Pathway                    | 0.3822                 | 1                      | 0
| Notch Pathway                  | 0.9959                 | 0.0268                 | 6
| OxidativeStress_Nrf2 Pathway   | 0.9830                 | 0.0819                 | 5
| PI3K Pathway                   | 0.1541                 | 0.9636                 | 2
| RTK_RAS_MAP Pathway            | 0.9586                 | 0.2179                 | 10
| TGF Beta Pathway               | 0.9601                 | 0.3752                 | 1
| P53 Pathway                    | 0.8994                 | 0.3936                 | 10
| betaCatenina_Wnt Pathway       | 0.9999                 | 0.0027                 | 5
| DDR Pathway                    | 0.9999                 | 0.0016                 | 8

Overall, with a median follow-up of 22 months (m), mPFS was 9.9m, and mOS was 10.6 m.