Sotorasib-induced liver and non-liver toxicity associated with sequential sotorasib following anti-PD(L)1

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Introduction

• KRASG12C is found in 13 to 15% lung adenocarcinomas.
• Sotorasib is a first-in-class KRASG12C covalent inhibitor recently FDA and EMA-approved for the treatment of metastatic KRASG12C-mutant non-small cell lung cancer (NSCLC) patients (pt) who have progressed after at least one prior systemic therapy.1
• Targeted therapy with small molecule and anti-PD(L)1 sequence or combination are associated with adverse events (AE) excess.2 A recently published case report described a severe hepatitis on sotorasib in the setting of sequential sotorasib following anti-PD-L1.3

We speculate that sequential sotorasib following anti-PDL1 may be associated with higher toxicity.

We sought to describe sotorasib-related AEs in KRASG12C-mutant NSCLC who did or did not received sequential sotorasib following PDL-1.4

Table 1. Clinico-pathological characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Sotorasib group</th>
<th>PDL-1 group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median, range)</td>
<td>68 (27-86)</td>
<td>66 (26-86)</td>
<td>0.86</td>
</tr>
<tr>
<td>Female</td>
<td>50 (31%)</td>
<td>39 (30%)</td>
<td>0.16</td>
</tr>
<tr>
<td>Tobacco history</td>
<td>14 (9%)</td>
<td>14 (11%)</td>
<td>0.74</td>
</tr>
<tr>
<td>Alcohol history</td>
<td>15 (10%)</td>
<td>17 (14%)</td>
<td>0.47</td>
</tr>
<tr>
<td>Prior history of liver disease</td>
<td>5 (3%)</td>
<td>7 (6%)</td>
<td>0.47</td>
</tr>
</tbody>
</table>

Results

• We identified 102 pts with advanced KRASG12C-mutant NSCLC treated with sotorasib in participating centers, including 46 (45%) pts receiving sequential sotorasib following immune checkpoint inhibitor (ICI) (i.e. sequence group) and 56 (55%) pts who did not received sequential sotorasib following ICI (i.e. control group).
• Baseline clinic-pathological patients characteristics were similar in sequence and control group (Table 1).
• Most pts received an IC-ICI before sotorasib treatment (95/102, 93%) during clinical course, and all of them received anti-PD-L1/19/95/19. Sequence group pts received anti-PDL1-L1 at last 48 hours before sotorasib initiation.
• ICI exposure was not different in both groups, but time from last ICI infusion to sotorasib initiation was significantly shorter in sequence group (Table 2).

Sotorasib-related hepatitis

• As sotorasib-related liver AEs were enriched in sequence group, we conducted a analysis focused on liver AEs.
• Hepatitis was defined as AST or ALT or GGT or Alk P or total bilirubinemia elevation according to cut-off value defined by NCI-CTCAE classification.
• History of daily alcohol consumption was not significantly different in sequence and control group. History of hepatocellular disease was more frequent in control group (14/86 pts (16%) vs 5/46 pts (11%), respectively; p=0.05). Four cases of immune mediated auto-immune diseases were reported in control group (two hepatitis, one rheumatoid polyarthritis and one systemic lupus) and no in sequence group.
• Proportion of grade 1 and 2 liver AEs were similar in both sequence and control group (Table 3).

Grade 2 sotorasib-related AEs occurrence and time from last ICI infusion to sotorasib initiation

• Grade ≥ 1 sotorasib-related AEs were significantly higher in pts receiving last ICI infusion less than 90 days before sotorasib initiation (22/34 pts (65%) vs 18/68 pts (27%), respectively; p<0.001 (Figure 1A)).
• Grade ≥ 3 hepatitis rate was significantly higher in pts receiving last immunotherapy injection less than 90 days before sotorasib initiation (6/34 pts (18%) vs 3/68 pts (5%), respectively; p<0.05 (Figure 1B)).

Conclusion

• We show an association between grade ≥ 2 sotorasib-related AEs excess and sequential sotorasib following anti-PDL1. This grade ≥ 2 sotorasib-related AEs excess correlated to time of last ICI infusion to sotorasib initiation < 90 days.
• To date, the underlying biological explanation is unknown.
• This association needs to be further explored in independent dataset, especially from ongoing reports.
• Impact on sotorasib discontinuation and efficiency is ongoing in our database.

Table 2. Sotorasib related adverse event prevalence by grade

<table>
<thead>
<tr>
<th>Category</th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>All pts</td>
<td>46 (45%)</td>
<td>56 (55%)</td>
<td>102</td>
<td>102</td>
<td>102</td>
<td>102</td>
</tr>
<tr>
<td>%</td>
<td>45.0%</td>
<td>55.0%</td>
<td>100.0%</td>
<td>100.0%</td>
<td>100.0%</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Table 3. Frequency and severity of liver adverse events

Figure 1A. Grade ≥ 3 sotorasib-related AEs occurrence according to time from last immunotherapy infusion to sotorasib initiation

Figure 1B. Grade ≥ 3 hepatitis occurrence according to time from last immunotherapy infusion to sotorasib initiation

References

3. Béringuer B. "Sequential checkpoint inhibitor inclusion in NCT03121024. Preliminary data on sotorasib: case report and investigation on the underlying mechanisms of severe hepatitis." JTO 2021; 15(9): 619 (Figure 1).

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