Objective

This analysis investigated the incidence, timing and association with efficacy of immune-mediated adverse events (imAEs) in the Phase 3 TOPAZ-1 study of durvalumab plus gemcitabine and cisplatin in advanced biliary tract cancer (BTC).

Conclusions

Most imAEs were grade 1 or 2 and manageable, and imAEs did not lead to an increase in the number of participants discontinuing study treatment.

imAEs occurred most frequently within 3 months but could occur at any time during the study, with median time to onset that varied according to the type.

Durvalumab plus GemCis was associated with an overall survival (OS) benefit versus placebo plus GemCis, irrespective of the presence of imAEs.

Consistent with other studies, imAEs may be associated with greater OS benefit; however, participants were few for this analysis, and further investigation is warranted in this association.

imAEs could be managed based on the treatment guidelines; thus, people with BTC who experience imAEs can be considered for continued treatment with durvalumab plus GemCis.

Plain language summary

Why did we perform this research?
The analysis described here was performed to assess side effects associated with the immune system in the TOPAZ-1 study: how often they occurred, their timing in relation to treatment and if they were associated with the length of time participants with BTC remained alive after being treated with durvalumab plus GemCis anti-cancer therapy.

How did we perform this research?
Participants were treated with either durvalumab plus GemCis or placebo plus GemCis. Side effects were categorized as being associated with the immune system for analysis. They were counted and the time they began was recorded. The length of time participants remained alive was measured and linked to side effects associated with the immune system.

What were the findings of this research?
Side effects associated with the immune system were mild and did not lead to more participants stopping treatment. The timing of side effects associated with the immune system varied. Participants benefited from treatment with durvalumab plus GemCis, regardless of whether or not they experienced side effects associated with the immune system.

What are the implications of this research?
This research, alongside other research from the TOPAZ-1 study, supports durvalumab plus GemCis as a first treatment for advanced BTC.

Where can I access more information?
Information about the medicines being used in this study and the people who could participate can be found here: https://clinicaltrials.gov/ct2/results?term=FC701251 Previous results from this study can be found here: https://evidence.nejm.org/0409026266015

Tables

Table 1. Incidence of immune-mediated adverse events

<table>
<thead>
<tr>
<th>Adverse event category</th>
<th>Durvalumab + GemCis</th>
<th>Placebo + GemCis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenal insufficiency</td>
<td>10 (2.9)</td>
<td>9 (2.8)</td>
</tr>
<tr>
<td>Dermatitis / rash</td>
<td>28 (8.3)</td>
<td>25 (7.7)</td>
</tr>
<tr>
<td>Hepatic events</td>
<td>9 (2.6)</td>
<td>7 (2.1)</td>
</tr>
<tr>
<td>Hypothyroid events</td>
<td>12 (3.5)</td>
<td>14 (4.3)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>8 (2.4)</td>
<td>6 (1.8)</td>
</tr>
<tr>
<td>Pancreatic events</td>
<td>2 (0.6)</td>
<td>4 (1.2)</td>
</tr>
<tr>
<td>Other rare / miscellaneous</td>
<td>14 (4.1)</td>
<td>14 (4.2)</td>
</tr>
</tbody>
</table>

Figure 1. Time to onset (A, B) and resolution (C, D) of immune-mediated adverse events by AE severity

Figure 2. Incidence of immune-mediated adverse events with all-time occurrence

Figure 3. Persistant participants with immune-mediated adverse events over time

Figure 4. Overall survival for immune-mediated adverse event occurrence in the durvalumab arm

Figure 5. Overall survival by immune-mediated adverse event occurrence in the placebo arm

Methods

TOPAZ-1 was a randomised, double-blind, global, Phase 3 study evaluating the efficacy and safety of durvalumab plus GemCis as first-line treatment for participants with advanced BTC.

imAEs are All of special / possible interest linked to drug exposure with a high immune-mediated mechanism and no clear alternative explanation – incidence of imAEs were calculated by programme adjudication – OS based rate (HR) was calculated using a Cox model with treatment as the only covariate, and imAE OS was calculated using the Kaplan-Meier method.

References