Cisplatin-related immunomodulation and efficacy with atezolizumab + cisplatin- vs carboplatin-based chemotherapy in metastatic urothelial cancer

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Immunomodulatory effects may underlie favourable outcomes with cisplatin ± atezo vs carboplatin ± atezo in mUC

- Cisplatin, but not carboplatin, achieves durable control of mUC in a subset of patients\(^1\)
- Atezo + cisplatin-based chemo was associated with better efficacy than atezo + carboplatin-based chemo in an exploratory subset analysis from IMvigor130\(^2\)
- Together, these findings raise the hypothesis that cisplatin may be associated with specific favourable immunomodulatory effects

### Phase III IMvigor130 study (N=1213)
- Locally advanced or metastatic UC
- No prior systemic therapy for mUC

#### OS by investigator's choice of platinum\(^2\)

<table>
<thead>
<tr>
<th></th>
<th>Arm A</th>
<th>Arm C</th>
</tr>
</thead>
<tbody>
<tr>
<td>mOS, mo</td>
<td>16.1</td>
<td>13.4</td>
</tr>
<tr>
<td>n</td>
<td>451</td>
<td>400</td>
</tr>
<tr>
<td>OS HR (95% CI)</td>
<td>0.85</td>
<td>0.85</td>
</tr>
<tr>
<td></td>
<td>0.73</td>
<td>0.91</td>
</tr>
</tbody>
</table>

- Favours Arm A (atezo + plt/gem)
- Favours Arm C (pbo + plt/gem)

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Effects of cisplatin ± atezolizumab on OS are most prominent in patients with PD-L1 IC–high tumours

**IMvigor130: OS by PD-L1 status and chemo**

<table>
<thead>
<tr>
<th>PD-L1 Status</th>
<th>Arm A: atezolizumab + cisplatin/gemcitabine</th>
<th>Arm C: placebo + cisplatin/gemcitabine</th>
<th>Arm C: placebo + carboplatin/gemcitabine</th>
</tr>
</thead>
<tbody>
<tr>
<td>IC0/1</td>
<td>mOS: 19.5 months (NR)</td>
<td>mOS: 12.8 months</td>
<td>mOS: 13.0 months</td>
</tr>
<tr>
<td>IC2/3</td>
<td>mOS: 27.9 months</td>
<td>mOS: 14.0 months</td>
<td>mOS: 14.0 months</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.46 (0.25, 0.83)</td>
<td>0.51 (0.30, 0.86)</td>
<td>1.00 (0.71, 1.42)</td>
</tr>
</tbody>
</table>

**PD-L1 expression on tumour-infiltrating immune cells**

- IC0/1: PD-L1–expressing immune cells on <5% of the tumour area
- IC2/3: ≥5% of the tumour area

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Does cisplatin vs carboplatin show evidence of immunogenic cell death?

**Immunogenic cell death**

- Chemotherapy
- Tumour
- PBMC

**IMvigor130 PBMC analyses**

<table>
<thead>
<tr>
<th></th>
<th>C1D1</th>
<th>C3D1</th>
<th>Total no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm A: atezo + cis/gem</td>
<td>14</td>
<td>14</td>
<td>28</td>
</tr>
<tr>
<td>Arm A: atezo + carbo/gem</td>
<td>24</td>
<td>24</td>
<td>48</td>
</tr>
<tr>
<td>Arm C: pbo + cis/gem</td>
<td>17</td>
<td>17</td>
<td>34</td>
</tr>
<tr>
<td>Arm C: pbo + carbo/gem</td>
<td>16</td>
<td>16</td>
<td>32</td>
</tr>
<tr>
<td><strong>Total no.</strong></td>
<td>71</td>
<td>71</td>
<td>142</td>
</tr>
</tbody>
</table>

- **scRNAseq**
- **No. of samples**

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a Only patients with evaluable samples at both C1D1 and C3D1 are included.

b Includes gene set enrichment analysis (Hallmark pathways).

c Includes samples from an MIBC non-trial cohort¹,²


- **Neoadjuvant MIBC cohort**: To study cis-related changes in the tumour microenvironment, gene expression data from 113 paired pre-/post-neoadjuvant cis/gem-treated samples were also analysed.

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Galsky M. IMvigor130 cisplatin biomarkers. Abstract 4107. https://bit.ly/3jB8jRR @MattGalsky | Content of this presentation is copyrighted to and the responsibility of the author. Permission is required for re-use.
Cisplatin vs carboplatin leads to gene expression changes suggestive of induction of innate and adaptive immunity

- **IMvigor130**: Cis- vs carbo-treated patients showed on-treatment enrichment of TNF-α signalling via NFκB, inflammatory response gene sets and interferon response gene sets across immune cell clusters

- **Neoadjuvant cohort**: TNFα signaling via NFκB was also enriched in paired tumour samples (post- vs pre-cis/gem)

**Heatmaps include pathways significant in ≥3 cell types, with manual ordering (IMvigor130). Asterisks (*) in heatmap cells indicate significance defined by a false discovery rate <0.05. Ten cells per sample were required.**
Conclusions

• In this exploratory analysis from IMvigor130, PD-L1 IC2/3 status was associated with longer OS in cisplatin- but not carboplatin-treated patients with mUC

• Cisplatin- vs carboplatin-based chemo was associated with increased innate and adaptive immune gene expression—both in circulating immune cells in patients with mUC enrolled in IMvigor130 and in the TME in a neoadjuvant cisplatin + gemcitabine–treated MIBC cohort

• These data suggest that cisplatin + gemcitabine enhances anti-tumour immunity, particularly when combined with atezolizumab (i.e., as seen when comparing IMvigor130 Arms A and C), potentially through the induction of immunogenic cell death

• These data may provide fundamental insights regarding the mechanisms underlying durable disease control achieved in the subset of patients with mUC treated with cisplatin-based chemo ± atezolizumab
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