**A global, multicentre, open-label, randomised Phase II trial of tobemustine with or without tiragolumab vs atezolizumab in patients with untreated metastatic urothelial cancer ineligible for platinum-based chemotherapy**

**Shilpa Gupta, Omar Alhalabi, Javier Puente, Marcella Fassò, Omar Alhalabi, Javier Puente,**
**Shilpa Gupta, Thomas Powles, tasmin stottig with or without**

**Table 2. Key eligibility criteria**

<table>
<thead>
<tr>
<th>Key eligibility criteria</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥18 years</td>
<td>None</td>
<td>No prior chemotherapy in the last 28 days before randomisation.</td>
</tr>
<tr>
<td>ECOG PS 0-2</td>
<td>None</td>
<td>History of autoimmune disease or immune deficiency disorder.</td>
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<tr>
<td>History of specific cancers (e.g., prostate, lung, melanoma, renal pelvic cancers)</td>
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<tr>
<td>Patients with active autoimmune disease</td>
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<tr>
<td>Patients with active rheumatoid arthritis or active osteoarthritis.</td>
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</tbody>
</table>

**Table 1. Study endpoints**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Primary endpoint</th>
<th>Secondary endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival (OS)</td>
<td></td>
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<tr>
<td>Progression-free survival (PFS)</td>
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<tr>
<td>Disease control rate (converted OR, CR, or stable disease maintained for ≥12 weeks)</td>
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<tr>
<td>Incidence and severity of adverse events (AEs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient-reported outcomes (European Organisation for Research and Treatment of Cancer Item Library 187)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Safety pharmacology (PK) and incidence and impact of anti-drug antibodies (ADA) on exposure, safety and efficacy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relationship between serum concentration or PK parameters with safety and efficacy endpoints</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relationship between ADA status and efficacy, safety, PK or ADAs</td>
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<td></td>
</tr>
</tbody>
</table>

**Sample size determination**

- The estimated sample size of 240 patients (80 per arm) was calculated based on the comparison of the experimental arms and the control arm with regard to the primary endpoint (ORR) using the following formula:

\[
N = \frac{Z_{1-\alpha/2}^2 \times \pi(1-\pi)}{d^2}
\]

- With a power of 80% and a significance level of 0.05 (two-sided), the estimated sample size is 240 patients (80 per arm). The sample size was calculated using the equation above, with \(Z_{1-\alpha/2}\) representing the standard normal deviate corresponding to a two-tailed test of size 0.05, \(\pi\) representing the expected response rate in the control group, \(d\) representing the desired difference in response rates between the experimental and control groups, and \(N\) representing the sample size.

- The estimated sample size is 240 patients, 80 per arm, to achieve the desired power and significance level.

**REFERENCES**

7. ECOG PS 0-1 or 2

**DECLARATIONS OF INTEREST**

- All authors declare no conflicts of interest.

**ACKNOWLEDGEMENTS**

- The authors thank the following: Biostatisticians and Clinical Trial Coordinators. Additional authors are listed in the online Supplementary Information.

**CLINICAL TRIAL DESIGN**

**Patient eligibility**

- Patients will be enrolled at 83 sites across 15 countries or regions per Figure 2.
- The study start date was 13 April 2023, and the estimated study completion date is 30 December 2026.

**ENROLLMENT**

- Patients will be enrolled at 83 sites across 15 countries or regions per Figure 2.
- The study start date was 13 April 2023, and the estimated study completion date is 30 December 2026.

**EXPLORATORY ENDPOINTS**

- OS and PFS (18-month OS and PFS).
- Relationship of additional biomarkers with efficacy endpoints (ORR, PFS, OS) as well as with safety, PK, immunogenicity and other biomarkers.
- Relationship between serum concentrations or PK parameters with safety and efficacy endpoints.
- Relationship between ADA status and efficacy, safety, PK or ADA endpoints.

**Sample size determination**

- The estimated sample size of 240 patients (80 per arm) was calculated based on the comparison of the experimental arms and the control arm with regard to the primary endpoint (ORR).

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