ANTIBODY-DRUG CONJUGATES IN UROTHELIAL CANCER AND AN OVERVIEW IN OTHER GENITOURINARY CANCERS

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• Antibody Drug Conjugates (ADCs) are an emerging class of targeted anticancer drug delivery agent that confer selective and sustained cytotoxic drug delivery to tumours.

• ADCs are structured from three main structural units:
  – monoclonal antibody against a specific target
  – linker molecule
  – Payloads: cytotoxic agent or drug

• Selection of an appropriate target, a monoclonal antibody, cytotoxic payload, and the manner in which the antibody is linked to the payload are key determinants of the safety and efficacy of ADCs.
ANTIBODY-DRUG CONJUGATES FOR UROTHELIAL CANCERS
BACKGROUND

• Patients with mUC who progress after platinum-based chemotherapy and immune checkpoint inhibitors have poor outcomes and limited treatment options

• UC is characterised by the expression of multiple cell surface antigens suitable for specific therapeutic targeting with antibody-drug conjugates (ADCs)

• **Two ADCs** in advanced development for **advanced urothelial cancer**:  
  – **Enfortumab vedotin** (recently FDA approved)  
  – **Sacituzumab govitecan** (late stage development)
**Immuno-drug Conjugate**
- Antibody target: Nectin-4
- Linker: Protease Cleavable
- Payload: MMAE - microtubule disrupting agent

**EV-101 phase 1 study** – initial assessment of efficacy and safety:
- 112 patients
- ORR: 43%
- PFS: 5.4 months

MMAE, monomethyl auristatin E; ORR, objective response rate; PFS, progression free survival
**EV-201 STUDY DESIGN**

- Single arm, pivotal phase 2 trial

**Cohort 1**
- Prior PD-1/L1 inhibitor and platinum-based therapy
- Enrolment completed July 2018
- N=128\(^1\)

**Cohort 2**
- Prior PD-1/L1 inhibitor, platinum naïve, cisplatin ineligible
- Enrolment ongoing

**Enfortumab vedotin**
- 1.25 mg/kg IV on days 1, 8, and 15 of each 28-day cycle

**Primary endpoint:** ORR per RECIST v1.1 as determined by BICR

**Select secondary endpoints:**
- DOR
- PFS
- OS
- Safety

\(^1\)3 patients did not receive enfortumab vedotin treatment: one each due to clinical deterioration, patient decision, and low haemoglobin after enrolment

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BICR, blinded independent central review; DOR, duration of response; IV, intravenous; ORR, objective response rate; OS, overall survival; PD-1/L1, programmed cell death 1/programmed cell death ligand 1; PFS, progression free survival; RECIST, Response Evaluation Criteria in Solid Tumors

### EV-201: COHORT 1
#### DEMOGRAPHICS AND DISEASE CHARACTERISTICS

<table>
<thead>
<tr>
<th>Category</th>
<th>Patients (N=125)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Male sex, n (%)</strong></td>
<td>88 (70)</td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td></td>
</tr>
<tr>
<td>Median (min, max)</td>
<td>69 (40,84)</td>
</tr>
<tr>
<td>≥75 years, n (%)</td>
<td>34 (27)</td>
</tr>
<tr>
<td><strong>ECOG PS of 1, n (%)</strong></td>
<td>85 (68)</td>
</tr>
<tr>
<td><strong>Primary tumour location, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Bladder/other</td>
<td>81 (65)</td>
</tr>
<tr>
<td>Upper tract</td>
<td>44 (35)</td>
</tr>
<tr>
<td><strong>Number of prior systemic therapies</strong>, median (min, max)</td>
<td>3 (1, 6)</td>
</tr>
<tr>
<td>≥2 Bellmunt adverse prognostic factors</td>
<td>52 (42)</td>
</tr>
<tr>
<td><strong>Metastasis sites, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Lymph nodes only</td>
<td>13 (10)</td>
</tr>
<tr>
<td>Visceral disease</td>
<td>112 (90)</td>
</tr>
<tr>
<td>Liver</td>
<td>50 (40)</td>
</tr>
<tr>
<td><strong>PD-L1 status by combined positive score</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>78/120 (65)</td>
</tr>
<tr>
<td>≥10</td>
<td>42/120 (35)</td>
</tr>
</tbody>
</table>

1 Patients with 1 prior therapy had platinum and a PD-1/L1 inhibitor in combination;  
2 Five patients were not evaluable for PD-L1

ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed cell death ligand 1

EV-201 results highly consistent with phase 1 EV-101 trial in same patient population

<table>
<thead>
<tr>
<th>COHORT 1 ORR per RECIST v 1.1 assessed by BICR</th>
<th>Patients (N=125)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed objective response rate, n (%) 95% confidence interval&lt;sup&gt;1&lt;/sup&gt;</td>
<td>55 (44)</td>
</tr>
<tr>
<td></td>
<td>(35.1, 53.2)</td>
</tr>
<tr>
<td>Best overall response per RECIST v. 1.1, n (%)</td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>15 (12)</td>
</tr>
<tr>
<td>Partial response</td>
<td>40 (32)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>35 (28)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>23 (18)</td>
</tr>
<tr>
<td>Not evaluable&lt;sup&gt;2&lt;/sup&gt;</td>
<td>12 (10)</td>
</tr>
</tbody>
</table>

<sup>1</sup>Computed using the Clopper-Pearson method;  
<sup>2</sup>Includes 10 patients who discontinued study prior to post-baseline response assessment, 1 patient who had uninterpretable post-baseline assessment and 1 patient whose post-baseline assessment did not meet the minimum interval requirement for stable disease

BICR, blinded independent central review; RECIST, Response Evaluation Criteria In Solid Tumors
**EV-201: DURATION OF RESPONSE**

**EV-201: COHORT 1 DURATION OF RESPONSE WITH ENFORTUMAB VEDOTIN**

At the time of analysis, 44% of responders had ongoing responses.

Median time to response: 1.8 mo (range: 1.2–9.2)

Most responses identified at first assessment

BICR, blinded independent central review; CR, complete response; DOR, duration of response; PR, partial response

EV-201: TREATMENT RELATED ADVERSE EVENTS

<table>
<thead>
<tr>
<th>Cohort 1 Treatment-related AEs by preferred term in ≥20% of patients (any Grade)(^1,2)</th>
<th>Patients (N=125) n (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>≥Grade 3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>62 (50)</td>
<td>7 (6)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>61 (49)</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>55 (44)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>50 (40)</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>50 (40)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Nausea</td>
<td>49 (39)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>40 (32)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>28 (22)</td>
<td>0</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>28 (22)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Rash maculo-popular</td>
<td>27 (22)</td>
<td>5 (4)</td>
</tr>
</tbody>
</table>

- Most common adverse reactions (≥ 20%) included fatigue, peripheral neuropathy, decreased appetite, rash, alopecia, nausea, dysgeusia, diarrhea, dry eye, pruritus and dry skin\(^3\)
- Recommend holding treatment if blood glucose >250mg/dL\(^3\)
- Permanently discontinue for peripheral neuropathy ≥ grade 3\(^3\)

AEs, adverse events
MAXIMAL TARGET LESION REDUCTION BY PD-L1 STATUS AND BEST RESPONSE

- Responses observed regardless of PD-L1 expression level

OBJECTIVE RESPONSE RATE

Best overall response by RECIST v 1.1 (Investigator assessed), N=45

<table>
<thead>
<tr>
<th>Confirmed ORR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>73.3% (33/45)</td>
</tr>
<tr>
<td></td>
<td>(58.1, 85.4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CR</th>
<th>15.6% (7/45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>57.8% (26/45)</td>
</tr>
</tbody>
</table>

CI, confidence interval; CPS, combined positive score; CR, complete response; EV, enfortumab vedotin; mUC, metastatic urothelial carcinoma; ORR, objective response rate; PD-L1, Programmed death-ligand 1; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors
• Antibody target: Trop-2
• Linker: Hydrolysable linker
• Payload: SN-38-parent compound - irinotecan
• Trop-2 is an epithelial cell surface antigen highly expressed in UC
• Shown activity across multiple tumour types: NSCLC, SCLC, mTNBC

Humanised Anti-Trop-2 Antibody (hRS7)
- Directed towards Trop-2, an epithelial antigen expressed on many solid tumours

Linker for SN-38
- Hydrolysable linker for payload release
- High drug-to-antibody ratio (7.6:1)

SN-38 Payload
- Metabolite of topoisomerase I inhibitor
- SN-38 more potent than parent compound, irinotecan

ADC, antibody drug conjugate; mTNBC, metastatic triple-negative breast cancer; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; UC, urothelial cancer
SACITUZUMAB STUDIES

• **IMMU-132 Phase 1 study¹**
  – Initial assessment of efficacy and safety in 45 mUC patient's pts who progressed after ≥1 prior systemic therapy
  – ORR 31%
  – Grade ≥3 AEs in ≥5% of pts were neutropenia/neutrophil count decreased (38%), anaemia (11%), hypophosphatemia (11%), diarrhoea (9%), fatigue (9%), and febrile neutropenia (7%).

• **TROPHY-U-01: Phase 2 ongoing study²**
  – 35 patients post platinum and post CPI included in interim analysis
  – ORR 29%; CR 6%

**TROPHY-U-01: TRAE ≥ 20% ANY GRADE OR ≥ 5% GRADE ≥3 (N=35)**

<table>
<thead>
<tr>
<th>Category</th>
<th>Event</th>
<th>All Grades (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic</td>
<td>Neutropenia</td>
<td>66</td>
<td>29</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>Leukopenia</td>
<td>40</td>
<td>20</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Anaemia</td>
<td>34</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Febrile neutropenia</td>
<td>11</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Lymphocyte count decreased</td>
<td>11</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Diarrhoea</td>
<td>57</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>43</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
<td>20</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>General disorders &amp; administrative site conditions</td>
<td>Fatigue</td>
<td>54</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Infections &amp; infestations</td>
<td>Urinary tract infection</td>
<td>14</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Skin &amp; subcutaneous tissue</td>
<td>Alopecia</td>
<td>74</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Metabolism &amp; nutrition</td>
<td>Decreased appetite</td>
<td>20</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

AE, adverse event; CPI, checkpoint inhibitors; CR, complete response; ORR, objective response rate; TRAE, treatment related adverse event

CONCLUSIONS

- Immuno-drug conjugates are a new class of drugs in urothelial cancer
- Enfortumab vedotin approved in advanced or metastatic urothelial cancer post platinum, post checkpoint inhibitor
- Promising data of enfortumab in first line in combination with checkpoint inhibitors
- Ongoing studies with sacituzumab govitecan which targets Trop-2
- Await larger phase 3 confirmatory studies
ANTIBODY-DRUG CONJUGATES FOR OTHER GENITOURINARY CANCERS
ANTIBODY-DRUG CONJUGATES IN OTHER GU TUMOUR TYPES

• Prostate Cancer\(^1\)
  – Prostate-specific membrane antigen (PSMA) is over expressed on the surface of cancer cells and is therefore a suitable target for selective drug delivery through conjugated antibodies
  – There are a number of PSMA-ADC drugs in development for mCRPC that have shown promising activity in phase I/II trials
  – Clinical trials are ongoing to investigate the effects of sacituzumab govitecan which targets TROP-2 in patients with mCRPC (NCT03725761)\(^2\)

• Renal Cell Carcinoma\(^3\)
  – ENPP3 is a novel target specific to renal cell carcinoma (RCC) with minimal expression in normal tissue
    • ADCs targeting ENPP3 in initial human studies warrant further investigation
  – Other antigen targets for ADCs under investigation in RCC include: CD70, CD27L, TIM-1\(^4,5\)

ADC, Antibody drug conjugate; CD, cluster of differentiation; ENPP3, ectonucleotide pyrophosphatase/phosphodiesterase 3; GU, genitourinary; IL, interleukin; mCRPC, metastatic castration resistant prostate cancer; PSMA, prostate-specific membrane antigen; TIM-1, T-cell immunoglobulin and mucin domain 1
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