Immunoterapia nella malattia avanzata

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Systemic therapy for urothelial cancer - 5 new immunotherapeutic agents

- Paclitaxel (Ph II)²
- Docetaxel (Ph II)⁴
- MVAC (Ph II)³
- Gemcitabine + cisplatin (Ph III)⁸
- HD-MVAC (Ph III)⁸
- Gemcitabine + paclitaxel (Ph II)⁷
- Vinflunine (Ph III)⁹
- Gemcitabine + carboplatin vs MCaVi (Ph III)¹¹
- Gemcitabine + cisplatin + paclitaxel (Ph II)¹²
- Atezolizumab (Ph II)¹³
- Durvalumab (Ph I/Ii)¹⁴
- Avelumab (Ph I)¹⁷
- Nivolumab (Ph I/I)¹⁸
- Pembrolizumab (Ph I/I)¹⁹

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**Agencies & Action**

- Gemcitabine authorisation in UK (26 Oct 1995)³
- Gemcitabine EMA harmonisation (23 Sep 2008)⁹
- Vinflunine EMA approval (21 Sep 2009)¹⁰
- Durvalumab FDA approval (18 May 2016)¹⁷
- Pembrolizumab FDA/EMA approval (18 May 2016)¹¹
- Pembrolizumab FDA/EMA approval (18 May 2016)¹⁶
- Nivolumab FDA/EMA approval (2 Feb 2017)²¹
- Atezolizumab FDA approval (9 May 2017)¹⁵

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Five checkpoint inhibitors now approved for UC!

BCG

Atezolizumab (US/EU) (2L)

26-year gap

Atezolizumab (US/EU) (1L) cisplatin-ineligible

Nivolumab (US/EU) (2L)

Pembrolizumab (US/EU) (1L cisplatin-ineligible) (2L)

Vinflunine (EU only)

Durvalumab (US) (2L)

Avelumab (US) (2L)


1L, first-line; 2L, second-line;
BCG, Bacillus Calmette-Guérin vaccine; UC, urothelial carcinoma.
Rationale for immune checkpoint inhibitors in UC
Intravesical BCG is the first immunotherapy for NMIBC

BCG was the first immunotherapy to receive approval from the FDA for cancer treatment and remains the gold standard for NMIBC\(^1,2\)

- BCG is an attenuated form of *Mycobacterium bovis*, the bacterium that causes bovine tuberculosis\(^1\)
- The MOA of BCG is not yet completely understood, despite its long history of use in bladder cancer\(^1,3\)

Attachment to urothelial cells
Internalisation by bladder cancer cells
Antigen presentation and cytokine release by bladder cancer cells
Immune cell recruitment
Cytokine production
Immune-mediated cytotoxicity


BCG, Bacillus Calmette–Guerin vaccine; FDA, Food and Drug Administration; MOA, mechanism of action; NMIBC, non-muscle-invasive bladder cancer.
PD-L1 expression is associated with grade and stage in UC

**PD-L1 positivity increases with advancing local tumour stage in UC**

- pTa
- pT1
- pT2
- pT3/4
- Cis

**PD-L1 positivity is significantly associated with high tumour grade in UC**

- Low grade
- High grade

OR=2.4
(95% CI 1.20–4.72)
p=0.009

CI, confidence interval; OR, odds ratio; PD-L1, programmed death-ligand 1; UC, urothelial carcinoma.
Bladder cancer is considered to be a highly immunogenic tumour\(^1\)

1L metastatic setting
**Phase II IMvigor210 & KN052 Study Design and Objectives**

- **Key cohort 1 inclusion criteria:**
  - No prior treatment for mUC (> 12 months since perioperative chemotherapy)
  - ECOG PS 0-2
  - Cisplatin ineligibility based on ≥ 1 of the following: GFR < 60 and > 30 mL/min (Cockcroft-Gault), Grade ≥ 2 hearing loss (25 dB at 2 contiguous frequencies) or peripheral neuropathy, ECOG PS 2

- **Endpoints:**
  - Primary: confirmed ORR per RECIST v1.1 (central IRF)
  - Key secondary: DOR, OS, safety

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<table>
<thead>
<tr>
<th>Study</th>
<th>Agent</th>
<th>Phase and Type</th>
<th>Primary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>MK3475-361/KEYNOTE-361&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Pembrolizumab ± chemotherapy&lt;sup&gt;a&lt;/sup&gt; vs chemotherapy</td>
<td>3 Randomised, controlled</td>
<td>PFS, OS</td>
</tr>
<tr>
<td>IMvigor130&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Atezolizumab ± chemotherapy&lt;sup&gt;a&lt;/sup&gt; vs chemotherapy</td>
<td>3 Randomised, controlled</td>
<td>PFS, OS, % with AEs</td>
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<tr>
<td>DANUBE&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Durvalumab ± tremelimumab vs SOC chemotherapy</td>
<td>3 Randomised, open label</td>
<td>PFS, OS</td>
</tr>
<tr>
<td>CheckMate901&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Nivolumab+Ipilimumab vs chemotherapy</td>
<td>3 Randomised, open label</td>
<td>PFS, OS</td>
</tr>
</tbody>
</table>

<sup>a</sup> vs chemotherapy

<sup>1</sup> Galsky MD et al. TPS 539

<sup>2</sup>

<sup>3</sup>

<sup>4</sup>
≥2L metastatic setting
KEYNOTE-045: Phase III Pembrolizumab study in platinum refractory patients (n=542)

27% reduction in the risk of death

Total population

CPS ≥10%

Median OS months (95% CI)  HR (95% CI)  P
Pembrolizumab 10.3 (8.0–11.8)  0.73 (0.59–0.91)  0.0022
Chemotherapy  7.4 (6.1–8.3)  

CPS, combined positive score (defined as percentage of PD-L1+ tumor cells (TC) and infiltrating immune cells (IC) relative to the total number of TCHigh PD-L1 expression was defined as CPS ≥10%

Data cut-off date: September 7, 2016

Outcomes of IMvigor211 - Efficacy

US FDA and EMA approval for platinum-treated, advanced UC

Powles T. et al, Lancet 2017 & GU-ASCO 2018
## Immune checkpoint inhibitors in the platinum-refractory setting (no Head to Head comparisons)

<table>
<thead>
<tr>
<th></th>
<th>Atezolizumab(^1,6)</th>
<th>Nivolumab(^2)</th>
<th>Pembrolizumab(^3)</th>
<th>Avelumab(^4)</th>
<th>Durvalumab(^5)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase</strong></td>
<td>Phase II single arm</td>
<td>Phase II single arm</td>
<td>Phase III randomized</td>
<td>Phase Ib</td>
<td>Phase I/II</td>
</tr>
<tr>
<td><strong>Number of patients</strong></td>
<td>310(^1)</td>
<td>265</td>
<td>270</td>
<td>249</td>
<td>191</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>1200 mg q3w</td>
<td>3 mg/kg q3w</td>
<td>200 mg q3w</td>
<td>10 mg/kg q2w</td>
<td>10 mg/kg q2w</td>
</tr>
<tr>
<td><strong>ORR</strong></td>
<td>15%; lC2/3 23%</td>
<td>19.6%</td>
<td>21.1%</td>
<td>17%</td>
<td>17.8%</td>
</tr>
<tr>
<td><strong>Duration of response</strong></td>
<td>84% ongoing at median follow-up of 11.7 months/15.9 months</td>
<td>77% ongoing at median follow-up of 7.0 months</td>
<td>72% ongoing at median follow-up of 14.1 months</td>
<td>64% ongoing at data cut</td>
<td>Not reached at data cut</td>
</tr>
<tr>
<td><strong>Median OS</strong></td>
<td>7.9/11.1 months</td>
<td>8.7 months</td>
<td>10.3 months</td>
<td>7.7 months</td>
<td>18.2 months</td>
</tr>
<tr>
<td><strong>Median PFS</strong></td>
<td>2.1 months</td>
<td>2.0 months</td>
<td>2.1 months</td>
<td>1.5 months</td>
<td>1.5 months</td>
</tr>
<tr>
<td><strong>Grade 3/4 TRAEs</strong></td>
<td>16%(^1)/20%(^6)</td>
<td>18%</td>
<td>15% G3–5</td>
<td>10.8% G3–5</td>
<td>6.8%</td>
</tr>
</tbody>
</table>

Summary ≥2L

• Updated results confirm that clinical benefit with ICI use is maintained at long term

• Clinical prognostic factor models derived from non-comparative trials did support the benefit from ICI therapy compared to standard chemotherapy

• Results from translational studies will likely provide the basis for understanding patient outcome in this setting
How Emerging Clinical Data Will Impact the European/US Treatment Algorithm for Metastatic Urothelial Cancer

**FIRST LINE**
- **Yes**
  - PS 0-1
  - GFR ≥60 mL/min
  - **Standard chemotherapy:** GC, MVAC, HD-MVAC, PCG

- **No**
  - PS 2 or
  - GFR <60 mL/min
  - **Combination chemotherapy:** Carboplatin-based
  - **Immune checkpoint inhibitor**

**SECOND LINE**
- **PS 0-1**
  - **Standard second-line chemotherapy**
  - Consider immune checkpoint inhibitor therapy
- **PS ≥2**
  - **NO combination chemotherapy:** Monotherapy, BSC
  - Consider clinical trial

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BSC: best supportive care; GFR: glomerular filtration rate; (HD)MVAC: (high-dose) methotrexate, vinblastine, doxorubicin, cisplatin; PCG: paclitaxel, cisplatin, gemcitabine.

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