Immunotherapy for the Treatment of Kidney and Bladder Cancer

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Immunotherapy for Kidney and Bladder Cancer

Overview

Update of Recently Approved Therapies in First and Second Line Settings

Rationale for New Combination Therapies

Future Strategies
ALAN KOLETSKY, MD

Immunotherapy in Kidney & Bladder Cancers

Relevant Financial Relationships in the Past Twelve Months By Presenter or Spouse/Partner

Speakers Bureau: Astellas, BMS, Exelixis

The Speaker will Directly Disclosure The Use of Products For Which Are Not Labeled (e.g., Off Label Use) or if the Product is Still Investigational
Multiple Steps Required for Anticancer Activity

1. Multiple processes are required to establish and maintain an effective immune response.
2. Determinants of sensitivity and resistance not clearly defined yet.

- **Priming and activation**
  - Anti–CTLA-4
  - Anti-CD137 (agonist)
  - Anti-OX40 (agonist)
  - Anti-CD27 (agonist)
  - IL-2
  - IL-12

- **Cancer antigen presentation**
  - Vaccines
  - IFN-α
  - GM-CSF/T-VEC
  - Anti-CD40 (agonist)
  - TLR agonists

- **Release of cancer cell antigens**
  - Chemotherapy
  - Radiation therapy
  - Targeted therapy

- ** Trafficking of T cells to tumors**

- **Infiltration of T cells into tumors**
  - Anti-VEGF
  - Anti-CXCR4

- **Recognition of cancer cells by T cells**
  - CAR-T cell therapy
  - HDAC inhibitors

- **Killing of cancer cells and tolerance**
  - Anti–PD-1/PD-L1
  - IDO inhibitors
  - Anti–LAG-3

Tumor cells can inhibit the body’s immune response by binding to proteins, such as PD-1, on the surface of T cells; antibody therapies that block this binding reactivate the immune response.
Response Rate and Tumor Mutational Burden

Overcoming Immunotherapy Resistance

- Multiple strategies may be considered
- Tip balance away from tumor-protective mechanisms and towards antitumor immunity
- Rational combinations are required to move the field forward
- Some are leading to improved survival

Some possible combinations with immune checkpoint inhibitors

- Other immune checkpoint agents
- Chemotherapy
- Radiation
- Antiangiogenic therapy
- Targeted therapy
Targeting the PD-1/PD-L1 Axis Has Activity in GU Cancers

5 anti–PD-1/anti–PD-L1 drugs now approved for advanced urothelial carcinoma

- Atezolizumab, nivolumab, durvalumab, avelumab, pembrolizumab

Nivolumab approved for kidney cancer

Two positive phase 3 trials for combination therapy:
- Ipilimumab/nivolumab in first-line therapy
- Atezolizumab/bevacizumab as first-line therapy in PD-L1–positive tumors

Provocative data with enzalutamide-resistant cancers responding to pembrolizumab

Multiple large trials ongoing
Immunotherapy for the Treatment of Renal Cell Carcinoma
Approved Therapies for Renal Cell Carcinoma

New Options for Pretreated Patients

- Nivolumab
- Cabozantinib
- Lenvatinib + Everolimus
NCCN recommended parameters of risk stratification

Poor-Prognosis patients are defined as those with 3 or more predictors of short survival

Karnofsky performance score of 70 or less

Corrected Serum Calcium level $> 10 \text{ mg/dl} (2.5 \text{ mmol/liter})$

Lactate dehydrogenous level $> 1.5$ times upper limit of normal

Hemoglobin Level $< \text{ lower Limit of normal}$

Interval less than a year from original diagnosis to start of systemic therapy

2 or more sites of organ metastasis

*NCCN Guidelines 2013 Kidney Cancer*
CheckMate-025: Phase 3 Study of Nivolumab vs Everolimus

- **mRCC patients with clear-cell histology**
- **Prior antiangiogenic therapy**

N = 821

R

Nivolumab 3 mg/kg IV Q2W

Everolimus 10 mg PO daily

**Endpoints**
- **Primary**: OS
- **Secondary**: Response rate, PFS, effect of PD-L1 expression on OS, safety

CheckMate-025: Overall Survival\textsuperscript{1}


<table>
<thead>
<tr>
<th></th>
<th>Median OS, mo (95% CI)</th>
<th>No. of Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab (n = 410)</td>
<td>25.0 (21.8-NE)</td>
<td>183</td>
</tr>
<tr>
<td>Everolimus (n = 411)</td>
<td>19.6 (17.6-23.1)</td>
<td>215</td>
</tr>
</tbody>
</table>

HR = 0.73 (98.5% CI, 0.57-0.93), \( P < .002 \)

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CheckMate-025: Subgroup Analysis of OS

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Nivolumab</th>
<th>Everolimus</th>
<th>Unstratified Hazard Ratio for Death (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td>183/410</td>
<td>215/411</td>
<td>0.76 (0.62-0.92)</td>
</tr>
<tr>
<td><strong>MSKCC risk group</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Favorable</td>
<td>45/145</td>
<td>52/148</td>
<td>0.89 (0.59-1.32)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>101/201</td>
<td>116/203</td>
<td>0.76 (0.58-0.99)</td>
</tr>
<tr>
<td>Poor</td>
<td>37/64</td>
<td>47/60</td>
<td>0.47 (0.30-0.73)</td>
</tr>
<tr>
<td><strong>Prior anti-angiogenic regimens</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>128/294</td>
<td>158/297</td>
<td>0.71 (0.56-0.90)</td>
</tr>
<tr>
<td>2</td>
<td>55/116</td>
<td>57/114</td>
<td>0.89 (0.61-1.29)</td>
</tr>
<tr>
<td><strong>Region</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US/Canada</td>
<td>66/174</td>
<td>87/172</td>
<td>0.66 (0.48-0.91)</td>
</tr>
<tr>
<td>Western Europe</td>
<td>78/140</td>
<td>84/141</td>
<td>0.86 (0.63-1.16)</td>
</tr>
<tr>
<td>Rest of the world</td>
<td>39/96</td>
<td>44/98</td>
<td>0.78 (0.51-1.20)</td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>111/257</td>
<td>118/240</td>
<td>0.78 (0.60-1.01)</td>
</tr>
<tr>
<td>≥65 to &lt;75</td>
<td>53/119</td>
<td>77/131</td>
<td>0.64 (0.45-0.91)</td>
</tr>
<tr>
<td>≥75</td>
<td>19/34</td>
<td>20/40</td>
<td>1.23 (0.66-2.31)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>48/95</td>
<td>56/107</td>
<td>0.84 (0.57-1.24)</td>
</tr>
<tr>
<td>Male</td>
<td>135/315</td>
<td>159/304</td>
<td>0.73 (0.58-0.92)</td>
</tr>
</tbody>
</table>

## ORR by Risk Level

<table>
<thead>
<tr>
<th>MSKCC Risk Group</th>
<th>Nivolumab, %</th>
<th>Everolimus, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable</td>
<td>24</td>
<td>8</td>
</tr>
<tr>
<td>Intermediate</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td>Poor</td>
<td>27</td>
<td>3</td>
</tr>
</tbody>
</table>

Overall Survival by Tumoral PD-L1 Expression

Patients With ≥1% PD-L1 Expression

<table>
<thead>
<tr>
<th></th>
<th>Median OS, mo (95% CI)</th>
<th>No. of Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab (n = 94)</td>
<td>21.8 (16.5-28.1)</td>
<td>48</td>
</tr>
<tr>
<td>Everolimus (n = 87)</td>
<td>18.8 (11.0-19.9)</td>
<td>51</td>
</tr>
</tbody>
</table>

Patients With <1% PD-L1 Expression

<table>
<thead>
<tr>
<th></th>
<th>Median OS, mo (95% CI)</th>
<th>No. of Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab (n = 276)</td>
<td>27.4 (21.4-NE)</td>
<td>118</td>
</tr>
<tr>
<td>Everolimus (n = 299)</td>
<td>21.2 (17.7-26.2)</td>
<td>150</td>
</tr>
</tbody>
</table>

CheckMate-025: Duration of Response

Response Rate
Nivolumab 21.5%
Everolimus 3.9%

DOR
Nivolumab 23.0 months
Everolimus 13.7 months

Number of patients with durable benefit off therapy
Optimal duration of therapy unknown

Tumor Flare With Immunotherapy

In patients on immunotherapy, tumor flare or the appearance of new lesions may precede antitumor effects.

- This phenomenon may be characterized as a RECIST-defined progression and may result in premature discontinuation of therapy.

CheckMate-025: Treatment Beyond Progression

METEOR: Phase 3 Study of Cabozantinib vs Everolimus

Eligibility criteria
- mRCC with clear-cell component
- At least one prior VEGFR TKI
- Progression on or after prior VEGFR TKI within 6 months of study enrollment
- Karnofsky PS ≥70

Stratification: MSKCC risk criteria; number of prior VEGFR TKIs

Treatment until loss of clinical benefit or intolerable toxicity
Treatment beyond progression was permitted, if drug was tolerable and clinical benefit was noted

Primary endpoint: PFS
Secondary endpoints: OS, ORR
Exploratory endpoints: Safety, tolerability, tumour MET status, circulating tumour cells, serum bone markers and plasma biomarkers, skeletal-related events, and HRQOL


N = 658
METEOR: OS$^{1,a}$

<table>
<thead>
<tr>
<th></th>
<th>Median OS, mo (95% CI)</th>
<th>No. of Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabozantinib (n = 330)</td>
<td>21.4 (18.7-NE)</td>
<td>140</td>
</tr>
<tr>
<td>Everolimus (n = 328)</td>
<td>16.5 (14.7-18.8)</td>
<td>180</td>
</tr>
</tbody>
</table>

HR = 0.66 (95% CI, 0.53-0.83), $P = .00026$

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**Graph:**
- Probability of OS vs Months
- Cabozantinib vs Everolimus

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**Table:**

<table>
<thead>
<tr>
<th></th>
<th>No at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabozantinib</td>
<td>330 318 296 264 239 178 105 41 6 3 0</td>
</tr>
<tr>
<td>Everolimus</td>
<td>328 307 262 229 202 141 82 32 8 1 0</td>
</tr>
</tbody>
</table>

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$a$ Cut-off: December 31, 2015.

Lenvatinib Alone or Plus Everolimus vs Everolimus Randomized Phase 2 Trial

Primary endpoint: PFS
Secondary endpoints: OS, ORR, and safety

Eligibility criteria:
• Advanced or mRCC with clear-cell component
• One prior VEGF-targeted therapy
• ECOG PS 0 or 1
N = 153

R

1:1:1

Lenvatinib + everolimus
18 mg + 5 mg orally QD

Lenvatinib
24 mg orally QD

Everolimus
10 mg orally QD

### Phase 2 Lenvatinib Plus Everolimus: Efficacy

<table>
<thead>
<tr>
<th>Primary Analysis</th>
<th>Lenvatinib + Everolimus (n = 51)</th>
<th>Lenvatinib (n = 52)</th>
<th>Everolimus (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, mo</td>
<td>12.8 (7.4-17.5)</td>
<td>9.0 (5.6-10.2)</td>
<td>5.6 (3.6-9.3)</td>
</tr>
<tr>
<td>(95% CI)(^1,a)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median OS, mo</td>
<td>25.5 (20.8-25.5)</td>
<td>18.4 (13.3-NE)</td>
<td>17.5 (11.8-NE)</td>
</tr>
<tr>
<td>(95% CI)(^2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR, n (%)(^1,a)</td>
<td>18 (35)</td>
<td>20 (39)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Median duration of response, mo</td>
<td>13.1 (3.8-NE)</td>
<td>7.5 (3.8-NE)</td>
<td>8.5 (7.5-9.4)</td>
</tr>
<tr>
<td>(95% CI)(^2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median number of cycles (range)(^2)</td>
<td>9.0 (1-25)</td>
<td>8.5 (1-25)</td>
<td>5.0 (1-22)</td>
</tr>
</tbody>
</table>

\(^a\) As assessed by an independent radiologic review.

Key Points: Second-Line Therapy

- Level 1 data supports use of nivolumab OR cabozantinib
- Toxicities vary between VEGF pathway– versus PD-1 pathway–directed therapy
- No clear evidence for clinical choice
- No definitive biomarkers
- Role of additional combinations being tested
- Phase 3 confirmatory trial of lenvatinib + everolimus pending
What About Front-Line Therapy?
Is CTLA-4 Blockade Synergistic With Anti–PD-1?¹


1. Release of cancer cell antigens
2. Cancer antigen presentation
3. Priming and activation
4. Trafficking of T cells to tumors
5. Infiltration of T cells into tumors
6. Recognition of cancer cells by T cells
7. Killing of cancer cells

CTLA-4 blockade
PD-1/PD-L1 blockade

Circulation diagram showing steps in the immune response including:
- Cancer antigen presentation
- Priming and activation
- Trafficking of T cells to tumors
- Infiltration of T cells into tumors
- Recognition of cancer cells by T cells
- Killing of cancer cells
CheckMate-214: Phase 3 Trial

Eligibility criteria
- Treatment naïve advanced or metastatic clear-cell RCC
- Measurable disease
- Karnofsky PS ≥70
- Tumor tissue available for PD-L1 testing
N = 847

1: Nivolumab + ipilimumab
   - 3 mg/kg nivolumab + 1 mg/kg ipilimumab
   - Q3W for 4 cycles

2: Nivolumab
   - 3 mg/kg Q2W

3: Sunitinib
   - 50 mg orally QD
   - 4 weeks (6 week cycles)

Treatment until progression or unacceptable toxicity

3 Co-primary outcomes: PFS, OS, ORR

CheckMate-214: ORR per IRCC
IMDC Intermediate-Risk/Poor-Risk Patients

<table>
<thead>
<tr>
<th>Outcome (N = 847)</th>
<th>Nivolumab + ipilimumab (n = 425)</th>
<th>Sunitinib (n = 422)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed ORR, a % (95% CI)</td>
<td>42 (37–47)</td>
<td>27 (22–31)</td>
</tr>
<tr>
<td><strong>P</strong> &lt; .0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confirmed BOR, a %</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Complete response</strong></td>
<td>9 b</td>
<td>1 b</td>
</tr>
<tr>
<td>Partial response</td>
<td>32</td>
<td>25</td>
</tr>
<tr>
<td>Stable disease</td>
<td>31</td>
<td>45</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>20</td>
<td>17</td>
</tr>
<tr>
<td>Unable to determine/not reported</td>
<td>8</td>
<td>12</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median Duration of Response, Months (95% CI)</th>
<th>Patients With Ongoing Response, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab + ipilimumab</td>
<td>18.2 (14.8–NE)</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>NR (21.8–NE)</td>
</tr>
</tbody>
</table>

a IRRC-assessed ORR and BOR by RECIST v1.1. b P < 0.0001.
CheckMate-214: PFS per IRRC
IMDC Intermediate-Risk/Poor-Risk Patients

<table>
<thead>
<tr>
<th></th>
<th>Median PFS (95% CI), mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab + ipilimumab</td>
<td>11.6 (8.7-15.5)</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>8.4 (7.0-10.8)</td>
</tr>
<tr>
<td>HR = 0.82 (99.1% CI, 0.64-1.05), P &lt; .0331</td>
<td></td>
</tr>
</tbody>
</table>

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab + ipilimumab</td>
<td>425 304 233 187 163 149 118 46 17 3 0</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>422 282 191 139 107 86 57 33 11 1 0</td>
</tr>
</tbody>
</table>

CheckMate-214: OS
IMDC Intermediate-Risk/Poor-Risk Patients

<table>
<thead>
<tr>
<th></th>
<th>Median OS (95% CI), mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab + ipilimumab</td>
<td>NR (28.2-NE)</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>26.0 (22.1-NE)</td>
</tr>
</tbody>
</table>

HR = 0.63 (99.8% CI, 0.44-0.89), P < .00001

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>425</th>
<th>399</th>
<th>372</th>
<th>348</th>
<th>332</th>
<th>318</th>
<th>300</th>
<th>241</th>
<th>119</th>
<th>44</th>
<th>2</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab + ipilimumab</td>
<td>422</td>
<td>387</td>
<td>352</td>
<td>315</td>
<td>288</td>
<td>253</td>
<td>225</td>
<td>179</td>
<td>89</td>
<td>34</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Sunitinib</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**CheckMate 214: ORR and PFS per IRRC**

**IMDC Favorable Risk**

<table>
<thead>
<tr>
<th>Outcome, N = 249&lt;sup&gt;a&lt;/sup&gt;</th>
<th><strong>Nivolumab + Ipilimumab</strong> (n = 125)</th>
<th><strong>Sunitinib</strong> (n = 124)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed ORR,&lt;sup&gt;b&lt;/sup&gt; % (95% CI)</td>
<td>29 (21–38)</td>
<td>52 (43–61)</td>
</tr>
<tr>
<td>PFS,&lt;sup&gt;c&lt;/sup&gt; median (95% CI), months</td>
<td>15.3 (9.7–20.3)</td>
<td>25.1 (20.9–NE)</td>
</tr>
<tr>
<td>HR (99.1% CI)</td>
<td>2.18 (1.29–3.68)</td>
<td></td>
</tr>
<tr>
<td><em>P</em></td>
<td>.0002</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> 11% of patients in both arms had tumor PD-L1 expression ≥1%.  
<sup>b</sup> IRRC assessed by RECIST v1.1.  
<sup>c</sup> IRRC assessed.

# CheckMate-214: Treatment-Related Adverse Events

<table>
<thead>
<tr>
<th>Event, %</th>
<th>Nivolumab + Ipilimumab (n = 547)</th>
<th>Sunitinib (n = 535)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3–5</td>
</tr>
<tr>
<td>Treatment-related adverse events in ≥25% of patients</td>
<td>93</td>
<td>46</td>
</tr>
<tr>
<td>Fatigue</td>
<td>37</td>
<td>4</td>
</tr>
<tr>
<td>Pruritus</td>
<td>28</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>27</td>
<td>4</td>
</tr>
<tr>
<td>Nausea</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>16</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Palmar-plantar erythrodysesthesia syndrome</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Treatment-related AEs leading to discontinuation, %</td>
<td>22</td>
<td>15</td>
</tr>
</tbody>
</table>

<sup>a</sup> Two patients had grade 5 cardiac arrest. <sup>b</sup> Pneumonitis, immune-mediated bronchitis, lower GI hemorrhage, hemophagocytic syndrome, sudden death, liver toxicity, lung infection. <sup>c</sup> Cardiac arrest (n = 2), heart failure, multiple organ failure.

## CheckMate-214: Treatment-Related Adverse Events

<table>
<thead>
<tr>
<th>Event, %</th>
<th>Nivolumab + Ipilimumab (n = 547)</th>
<th>Sunitinib (n = 535)</th>
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<tbody>
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<td>Treatment-related adverse events in ≥25% of patients</td>
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<tr>
<td>Pruritus</td>
<td>28</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>37</td>
<td>4</td>
</tr>
<tr>
<td>Nausea</td>
<td>16</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>16</td>
<td>33</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Palmar-plantar erythrodysesthesia syndrome</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Treatment-related AEs leading to discontinuation, %</td>
<td>22</td>
<td>15</td>
</tr>
</tbody>
</table>

<sup>a</sup> Two patients had grade 5 cardiac arrest. <sup>b</sup> Pneumonitis, immune-mediated bronchitis, lower GI hemorrhage, hemophagocytic syndrome, sudden death, liver toxicity, lung infection. <sup>c</sup> Cardiac arrest (n = 2), heart failure, multiple organ failure.

CABOSUN: Randomized Phase 2 Assessment of Front-Line Cabozantinib

Multicenter, randomized, phase 2 study

- Clear-cell RCC
- Intermediate or poor risk
- No prior systemic therapy
  N = 157

Stratified by:
- International Metastatic Renal Cell Carcinoma Database Consortium risk group (intermediate vs poor)
- Bone metastasis (yes/no)

Cabozantinib 60 mg/d (Continuous dosing) (n = 79)

Sunitinib 50 mg/d (4/2 dosing) (n = 78)

Primary endpoint: PFS

CABOSUN: PFS per IRC and OS\(^1,a\)

<table>
<thead>
<tr>
<th></th>
<th>Median PFS</th>
<th>No. of Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabozantinib (n = 79)</td>
<td>8.6 mo</td>
<td>43</td>
</tr>
<tr>
<td>Sunitinib (n = 78)</td>
<td>5.3 mo</td>
<td>49</td>
</tr>
</tbody>
</table>

HR = 0.48 (95% CI, 0.31-0.74)
\(P = .0008\) (2-sided)

Median OS: cabozantinib, 26.6 mo; sunitinib, 21.2 mo

\(^a\) Data cutoff: PFS, September 15, 2016; OS, July 1, 2017.

Is VEGF Inhibition Synergistic With Anti–PD-1?¹

Increases in CD8$^+$ T cells are observed with treatments

Patient 3, Female, 62 years old

- 83% (5/6) of bev + atezo RCC patients had increases in tumor CD8$^+$ T cells
- 11% (1/9) of RCC patients had increased tumor CD8$^+$ T cells following monotherapy atezo (PCD4989g)

Wallin et al, Nat Comm, 2016
Phase 2 IMmotion150 Trial Design\textsuperscript{1,2}

- Treatment naive, locally advanced, or metastatic RCC
- \textbf{N} = 305

\begin{itemize}
  \item IMmotion150 was designed to be hypothesis generating and inform the phase 3 study IMmotion151
  \item Co-primary endpoints were PFS (RECIST v1.1 by IRF) in ITT patients and patients with \textgtr=1\% of IC expressing PD-L1
  \item Exploratory endpoints included interrogation of the association between outcome and TME gene signatures\textsuperscript{3}
\end{itemize}

\textsuperscript{a} Crossover from atezolizumab monotherapy not allowed in Europe.

Bevacizumab + Atezolizumab – Phase 2 Efficacy


INV PFS ITT imRECIST

- Atezo + bev
- Atezo
- Sunitinib
- Censored

Atezo: 8.5 mo (7.9-13.6)
Sunitinib: 9.9 mo (7.0-14.1)
Atezo + bev: 17.3 mo (11.6-24.9)

Atezo + bev vs sunitinib
HR = 0.76 (95% CI, 0.55-1.11)

No. at risk
Atezo + bev 101 73 54 44 33 10 2
Atezo 103 56 34 28 25 11 2
Sunitinib 101 59 37 26 18 7 1

INV PFS PD-L1+ imRECIST

- Atezo + bev
- Atezo
- Sunitinib
- Censored

Sunitinib: 8.4 mo (5.8-11.3)
Atezo: 10.9 mo (5.4-14.0)
Atezo + bev: 21.9 mo (11.1-27.6)

Atezo + bev vs sunitinib
HR = 0.47 (95% CI, 0.29-0.78)

No. at risk
Atezo + bev 50 37 27 22 19 5 2
Atezo 54 28 17 14 14 6 –
Sunitinib 60 35 20 14 8 3 –
IMmotion151: Phase 3 Assessment of Bevacizumab/Atezolizumab

- Treatment-naïve advanced or metastatic RCC
- Clear-cell and/or sarcomatoid histology
- KPS ≥ 70
- Tumor tissue available for PD-L1 staining

N = 915

Stratification:
- MSKCC risk score
- Liver metastases
- PD-L1 IC IHC status (< 1% vs ≥ 1%)

Co-primary endpoints: Investigator-assessed PFS in patients with PD-L1 expression ≥1; OS in ITT population

Atezolizumab 1200 mg IV + Bevacizumab 15 mg/kg Q3W

Sunitinib 50 mg (4 wk on, 2 wk off)

# IMmotion151: Efficacy and Safety

<table>
<thead>
<tr>
<th></th>
<th>PD-L1+ (n = 362)^a</th>
<th></th>
<th></th>
<th>ITT (N = 915)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sunitinib (n = 184)</td>
<td>Atezolizumab + Bevacizumab (n = 178)</td>
<td>Sunitinib (n = 461)</td>
<td>Atezolizumab + Bevacizumab (n = 454)</td>
</tr>
<tr>
<td>mPFS (95% CI)</td>
<td>7.7 (6.8-9.7)</td>
<td>11.2 (8.9-15.0)</td>
<td>8.4 (7.5-9.7)</td>
<td>11.2 (9.6-13.3)</td>
</tr>
<tr>
<td>HR (95% CI), P</td>
<td>0.74 (0.57-0.96), 0.0217</td>
<td>0.83 (0.70-0.97), 0.219^b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR, %</td>
<td>35 (28-42)</td>
<td>43 (35-50)</td>
<td>33 (29-38)</td>
<td>37 (32-41)</td>
</tr>
<tr>
<td>DOR, months (95% CI)</td>
<td>1.29 (9.8-NE)</td>
<td>NE (12.4-NE)</td>
<td>14.2 (11.3-NE)</td>
<td>16.6 (15.4-NE)</td>
</tr>
</tbody>
</table>

Treatment-related grade 3-4 AEs: 40% atezolizumab/bevacizumab; 54% sunitinib
Treatment-related any grade AE leading to discontinuation: 12% atezolizumab/bevacizumab; 8% sunitinib

^a PD-L1 expression on ≥1% on tumor infiltrating immune cells, SP142 IHC assay. ^b Descriptive purposes only.

VEGFR-TKI + Anti–PD-1:
Axitinib + Pembrolizumab—Efficacy

N = 52

Axitinib + Pembrolizumab
Pts with baseline assessment 52 (100)
Pts with measurable disease at BL 52 (100)

Best overall response, n (%)

- CR 3 (5.8)
- PR 34 (65.4)
- Stable disease 10 (19.2)
- Progressive disease 2 (3.8)
- Indeterminate\(^b\) 3 (5.8)

ORR (CR + PR) 37 (71.2)
95% exact CI 56.9-82.9

UPDATED ORR\(^2\) 73.1%

- Median PFS was 15.1 mo (11.4-NR) in overall population
- UPDATED PFS: 20.9 months\(^2\)
- Of 11 pts enrolled in the dose-finding phase, median PFS not yet reached
- 9 of 48 (18.8%) evaluable tumor specimens were PD-L1–positive

\(^a\) Stable disease or PR not confirmed. \(^b\) 2 patients indeterminate and 1 patient with no follow-up assessment.

VEGFR-TKI + Anti–PD-1: Axitinib + Pembrolizumab—Safety

The picture can't be displayed.

Update²

- Most common grade ≥ 3 AEs
  - Hypertension (23%), diarrhea (10%), fatigue (10%)
- Immune-related AEs
  - Diarrhea (29%), increased ALT 17%, increased AST(13%), hypothyroidism (13%), fatigue (12%)

**Dosage**

<table>
<thead>
<tr>
<th>(N = 52)</th>
<th>Pembrolizumab</th>
<th>Axitinib</th>
<th>Days on Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>1.9 (0.1)</td>
<td>8.5 (1.7)</td>
<td>318.5 (124.7)</td>
</tr>
<tr>
<td>Median</td>
<td>2.0</td>
<td>8.9</td>
<td>316.0</td>
</tr>
<tr>
<td>Range</td>
<td>1.6-2.1</td>
<td>4.7-13.8</td>
<td>22.0-656.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AEs in ≥20% of Pts, n (%)</th>
<th>Immune-Related AEs, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>34 (65.4)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 (9.6)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (5.8)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>9 (17.3)</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>3 (5.8)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>PPE syndrome</td>
<td>2 (3.8)</td>
</tr>
<tr>
<td>Increased AST</td>
<td>2 (3.8)</td>
</tr>
<tr>
<td>Headache</td>
<td>4 (7.7)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>2 (3.8)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>3 (5.8)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Oral pain</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Colitis</td>
<td>2 (3.8)</td>
</tr>
</tbody>
</table>

a Dosage: 2 mg/kg IV pembrolizumab every 3 weeks + 5 mg axitinib twice daily. b No immune-related grade ≥4 AEs reported.

## First-Line Phase 3 Trials in Advanced RCC

<table>
<thead>
<tr>
<th>Experimental Arm</th>
<th>Primary Endpoint</th>
<th>Estimated N</th>
<th>Trial</th>
<th>ClinicalTrials.gov ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axitinib + avelumab</td>
<td>PFS</td>
<td>583</td>
<td>JAVELIN Renal 101</td>
<td>NCT02684006</td>
</tr>
<tr>
<td>Axitinib + pembrolizumab</td>
<td>PFS, OS</td>
<td>840</td>
<td>KEYNOTE-426</td>
<td>NCT02853331</td>
</tr>
<tr>
<td>Bevacizumab + atezolizumab</td>
<td>PFS, OS in PD-L1–detectable tumors</td>
<td>900</td>
<td>IMmotion151</td>
<td>NCT02420821</td>
</tr>
<tr>
<td>Nivolumab + ipilimumab</td>
<td>PFS, OS</td>
<td>1,070</td>
<td>CheckMate 214</td>
<td>NCT02231749</td>
</tr>
<tr>
<td>Nivolumab + cabozantinib or nivolumab + ipilimumab + cabozantinib</td>
<td>PFS in intermediate-risk/poor-risk patients</td>
<td>1,014</td>
<td>CheckMate 9ER</td>
<td>NCT03141177</td>
</tr>
<tr>
<td>Lenvatinib/pembrolizumab or lenvatinib/everolimus</td>
<td>PFS</td>
<td>735</td>
<td>CLEAR</td>
<td>NCT02811861</td>
</tr>
<tr>
<td>Sunitinib + AGS-003</td>
<td>OS</td>
<td>450</td>
<td>ADAPT</td>
<td>NCT01582672</td>
</tr>
</tbody>
</table>

Immunotherapy for the Treatment of Bladder Cancer
Immune Checkpoint Blockade Has Revolutionized the Treatment of Advanced Urothelial Carcinoma

• Before 2016, cytotoxic chemotherapy was the only option for patients with locally advanced or metastatic urothelial carcinoma.

• Cisplatin-based combination chemotherapy remains the standard of care for eligible patients.

• Outcomes with carboplatin-based chemotherapy are poor, with median survival about 9 months in phase 3 trials.

• After failure of platinum-based chemotherapy, survival was short, and available treatments (taxanes, pemetrexed, vinflunine [EU]) were toxic.

Proposed Criteria for Definition of Cis-Platinum Ineligible Patients for CDDP-Based Regimens

1. Poor Performance Status (ECOG 2 or higher)

2. CrCl <60 ml/min

3. Hearing Loss or Neuropathy (Grade 2 or Worse)

4. NYHA Class III Heart Failure
Rapid Development of Immunotherapy in Bladder Cancer

5 drugs approved in 13 months

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism</th>
<th>Schedule</th>
<th>Post Platinum</th>
<th>Frontline Cis Ineligible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atezolizumab</td>
<td>Anti–PD-L1</td>
<td>Q3W</td>
<td>Accelerated approval</td>
<td>Accelerated approval</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>Anti–PD-1</td>
<td>Q2W</td>
<td>Accelerated approval</td>
<td>-</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>Anti–PD-L1</td>
<td>Q2W</td>
<td>Accelerated approval</td>
<td>-</td>
</tr>
<tr>
<td>Avelumab</td>
<td>Anti–PD-L1</td>
<td>Q2W</td>
<td>Accelerated approval</td>
<td>-</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>Anti–PD-1</td>
<td>Q3W</td>
<td>Full approval</td>
<td>Accelerated approval</td>
</tr>
</tbody>
</table>
IMvigor210 Cohort 2 Study Design: Basis for Accelerated Approval\textsuperscript{1,2}

**IMvigor 210**
- Inoperable locally advanced or metastatic urothelial carcinoma
- Predominantly UC histology
- Tumor tissue evaluable for PD-L1 testing\textsuperscript{a}

Cohort 1 (N = 119)

1st-line cisplatin ineligible
Atezolizumab 1,200 mg IV every 3 wk until RECIST v1.1 progression

Cohort 2 (N = 310)

Platinum-treated mUC
Median follow-up: 17.5 mo (range: 0.2 to 21.1+)

Atezolizumab 1,200 mg IV every 3 wk until loss of clinical benefit

Co-primary endpoints:
- Confirmed ORR by RECIST v1.1 by central IRF
- ORR by investigator-assessed modified RECIST

Key secondary endpoints:
- DOR, PFS, OS, safety

\textsuperscript{a} PD-L1 prospectively assessed by a central laboratory, with patients and investigators blinded.
IMvigor210: Atezolizumab Approved for Prior Platinum-Treated Patients

- 40% had 2 or more prior regimens
- ORR: 14.8%
- Median OS: 7.9 mo
- Modest toxicity
- Higher levels of PD-L1 staining on immune cells are associated with higher response rate and longer survival (SP142 assay)

Atezolizumab Did Not Improve OS in the PD-L1–Positive Population

PD-L1 staining enriched for response and survival for both chemotherapy and atezolizumab

IMvigor211: Outcomes in the ITT Population

- Study design did not allow formal assessment of OS in the entire study population. HR and long-term survival favored atezolizumab.
- DOR was dramatically longer in patients treated with atezolizumab.

IMvigor211: Subgroup Analysis by Chemotherapy Type

OS was also examined in subgroups based on chemotherapy type at randomization:
- Improved OS was observed with atezolizumab vs taxanes.

### Subgroup Analysis:

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Median OS, mo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atezolizumab</td>
<td>8.3 mo (6.6-9.8)</td>
</tr>
<tr>
<td>Taxane</td>
<td>7.5 mo (6.7-8.8)</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>9.2 mo (7.9-10.4)</td>
</tr>
<tr>
<td>Vinflunine</td>
<td>8.3 mo (6.9-9.6)</td>
</tr>
</tbody>
</table>

1. Adapted from Powles T et al. European Association for Cancer Research, American Association for Cancer Research, and Italian Cancer Society (EACR-AACR-SIC) 2017 Special Conference. Abstract 606.
Atezolizumab is an active drug

- Phase 3 trial showed that vinflunine is a more active agent than previously thought
- Atezolizumab activity recapitulated earlier data

SP142 PD-L1 biomarker did not perform as predicted

- IC2/3 predicted both chemotherapy and immunotherapy response

Level 1 evidence (randomized phase 3 trial) supports pembrolizumab as second-line therapy
KEYNOTE-045 Phase 3 Trial (NCT02256436)¹

Key Eligibility Criteria
- Urothelial carcinoma of the renal pelvis, ureter, bladder, or urethra
- Transitional-cell predominant
- PD after 1-2 lines of platinum-based chemo or recurrence within 12 mo of perioperative platinum-based therapy
- ECOG PS 0-2
- Provision of tumor sample for biomarker assessment

N = 542

Stratification Factors
- ECOG PS (0/1 vs 2)
- Hemoglobin level (<10 vs ≥10 g/dL)
- Liver metastases (yes vs no)
- Time from last chemotherapy dose (<3 vs ≥3 mo)

n = 270

Pembrolizumab 200 mg IV Q3W for 2 y

n = 272

Paclitaxel 175 mg/m² Q3W, or Docetaxel 75 mg/m² Q3W, or Vinflunine 320 mg/m² Q3W

Key Endpoints
- **Primary:** OS and PFS in total and in PD-L1 combined positive score ≥10% populations
- **Secondary:** ORR and DOR in total and in PD-L1 combined positive score ≥10% populations; safety in total population

KEYNOTE-045: Pembrolizumab Improves OS vs Chemotherapy in the Second or Third Line

- Median OS 10.3 months for pembrolizumab vs 7.4 for chemo (HR = 0.73)
- Updated: 10.3 mo vs 7.3 mo (HR = 0.70)
- PFS short, and not different between the two arms
- PD-L1 expression with this assay was a poor prognostic biomarker and does not help with patient selection

KEYNOTE-045: Confirmed Objective Response Rate¹

Anti–CTLA-4 and Anti–PD-1: CheckMate-032: Study Design\textsuperscript{1,2}

Open-label, multicenter, phase 1/2 study

Pretreated patients with locally advanced or metastatic urothelial carcinoma

- Nivolumab 3 mg/kg IV every 2 wk (n = 78)\textsuperscript{1}
- Nivolumab 1 mg/kg + ipilimumab 3 mg/kg (NIVO 1 + IPI 3) IV every 3 wk for 4 cycles (n = 26)
- Nivolumab 3 mg/kg + ipilimumab 1 mg/kg (NIVO 3 + IPI 1) IV every 3 wk for 4 cycles (n = 104)

Nivolumab 3 mg/kg IV every 2 wk

- Treatment beyond progression was permitted if treatment was tolerated and prespecified clinical benefit was noted
- Tumor measurements: CT or MRI every 6 wk (±1 wk) from first dose for the first 24 wk, then every 12 wk (±1 wk)

# Anti–CTLA-4 and Anti–PD-1: CheckMate-032: Antitumor Activity

<table>
<thead>
<tr>
<th>Outcome, %</th>
<th>Nivolumab 1 + Ipilimumab 3 (n = 26)</th>
<th>Nivolumab 3 + Ipilimumab 1 (n = 104)</th>
<th>Nivolumab Monotherapy (n = 78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed ORR, %</td>
<td>38.5</td>
<td>26.0</td>
<td>24.4</td>
</tr>
<tr>
<td>95% CI</td>
<td>20.2-59.4</td>
<td>17.9-35.5</td>
<td>15.3-35.4</td>
</tr>
</tbody>
</table>

## Best overall response, %

<table>
<thead>
<tr>
<th>Response</th>
<th>Nivolumab 1 + Ipilimumab 3 (n = 26)</th>
<th>Nivolumab 3 + Ipilimumab 1 (n = 104)</th>
<th>Nivolumab Monotherapy (n = 78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>3.8</td>
<td>2.9</td>
<td>6.4</td>
</tr>
<tr>
<td>Partial response</td>
<td>34.6</td>
<td>23.1</td>
<td>17.9</td>
</tr>
<tr>
<td>Stable disease</td>
<td>19.2</td>
<td>25.0</td>
<td>28.2</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>26.9</td>
<td>41.3</td>
<td>38.5</td>
</tr>
</tbody>
</table>

Immune–Immune Combinations Hold Significant Promise

• CTLA-4, PD-1 pathway combinations have significant toxicity

• Identification of agents with less toxicity in combination is warranted
  – Advanced bladder cancer patients tend to be older and sicker

• Multiple different classes of agents are being tested
## Approved Checkpoint Inhibitors for Platinum-Refractory mUC

M Ornstein JTT online Feb 13, 2018 with permission

<table>
<thead>
<tr>
<th></th>
<th>Atezolizumab</th>
<th>Nivolumab</th>
<th>Pembrolizumab</th>
<th>Avelumab</th>
<th>Durvalumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase (no. of pts)</strong></td>
<td>Phase II (310)</td>
<td>Phase II (265)</td>
<td>Phase III (270)</td>
<td>Phase 1b (241)</td>
<td>I/II (191)</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>1200 mg Q 3wk</td>
<td>240 mg Q 2wk</td>
<td>200 mg Q 3wk</td>
<td>10mg/kg Q 2wk</td>
<td>10 mg/kg Q 2w</td>
</tr>
<tr>
<td><strong>ORR</strong></td>
<td>15%</td>
<td>24%</td>
<td>29%</td>
<td>18%</td>
<td>18%</td>
</tr>
<tr>
<td><strong>mPFS/OS (months)</strong></td>
<td>2.1/7.9</td>
<td>2.0/8.7</td>
<td>2.1/10.3</td>
<td>1.8/13.7</td>
<td>1.5/18.2</td>
</tr>
<tr>
<td><strong>Grade 3/4 Rx-Related AEs</strong></td>
<td>16%</td>
<td>18%</td>
<td>15%</td>
<td>8%</td>
<td>7%</td>
</tr>
<tr>
<td><strong>Most Common Rx-related AEs</strong></td>
<td>Fatigue (30%)</td>
<td>Fatigue (17%)</td>
<td>Pruritis (19.5%)</td>
<td>Infusion-related reaction (22.8%)</td>
<td>Fatigue (19.4%)</td>
</tr>
<tr>
<td></td>
<td>Nausea (14%)</td>
<td>Pruritis (9%)</td>
<td>Fatigue (13.9%)</td>
<td>Decrease appetite (9%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pruritis (10%)</td>
<td>Diarrhea (9%)</td>
<td>Nausea (10.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>FDA Approval</strong></td>
<td>May 18, 2016 (accelerated)</td>
<td>February 2, 2017 (accelerated)</td>
<td>May 18, 2017 (regular approval)</td>
<td>May 9, 2017 (accelerated)</td>
<td>May 1, 2017 (accelerated)</td>
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Future Strategies
Indoleamine 2,3-Dioxygenase 1 (IDO1)\(^1\)

Resistance to PD-1 pathway inhibition may be mediated in part by IDO1 activity

**IDO1:**
- Depletes tryptophan and increases kynurenine levels
- Leads to an immunosuppressive tumor microenvironment

This leads to:
- Decreased effector T-cell function
- Differentiation of regulatory T cells

Inhibitors of this pathway are being tested in mUC

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Epacadostat and Pembrolizumab

- 40 patients treated in expansion cohort at 100 mg PO BID
- ORR is 35%
- Tolerability appears similar to PD-1 therapy alone
- 80% had 1 or fewer prior regimens in metastatic setting
  - Relatively lightly pretreated cohort compared with IMvigor210 (59%), but similar to KEYNOTE-045 (80%) and Checkmate-275 (71%)
- Promising ORR worthy of further investigation in a planned large randomized trial

Nivolumab and BMS986205

25 bladder cancer patients treated in a multicohort phase 1/2a dose-escalation and expansion study (CA017-003)

ORR was 32%

Kynurenine levels were decreased in pre- and on-treatment tumor biopsies

Toxicity seemed similar to single agent therapy