Updates on the Role of Immunotherapy in mRCC and mUC

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National Cancer Centre Singapore
Disclosures

• Speaker Bureau: Pfizer, J&J, Sanofi, Novartis, MSD, Eisai, Astellas

• Advisory Board/ Consultant: GSK, Novartis, Bayer, J&J, Mundipharma, Astellas, MSD, BMS, Eisai, Amgen

• Research support: Sanofi, J&J, Astellas
Outline

• Immunotherapy in mRCC

• Immunotherapy in mUC

• Future Directions

• Summary
Rationale for Immunotherapy in RCC

- Spontaneous remissions attributed to the immune system of advanced RCC have been observed.¹
- RCC exhibits immune cell infiltrates, and several immune escape mechanisms have been reported in RCC.²,³
- Historically, the mainstay of treatment for patients with mRCC was immunotherapy with interleukin-2 or interferon-α.¹
- Immuno-Oncology (I-O) is an evolving treatment modality encompassing agents designed to directly harness the patient’s own immune system to fight cancer.⁷,⁸

Studies have documented alterations in various immune cell types in RCC, including³-⁶:

<table>
<thead>
<tr>
<th>Treg</th>
<th>CD45+ Memory T Cells</th>
<th>CD8+ T Cells</th>
<th>CD4+ T Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ levels: Poor prognosis</td>
<td>↑ levels: Fair/Poor prognosis</td>
<td>↑ levels: Fair/Poor prognosis/no association</td>
<td>↑ levels: Fair/Poor prognosis</td>
</tr>
</tbody>
</table>

RCC=renal cell carcinoma; mRCC=metastatic renal cell carcinoma; Treg=regulatory T cell.

RCC Treatment: Revolutionized in a Short Period of Time

- High-dose interleukin-2
  - Sorafenib (Dec 2005)

- Bevacizumab + IFN-α (Jul 2009)
  - Pazopanib (Oct 2009)

- Sunitinib (Jan 2006)
  - Temsirolimus (May 2007)
  - Everolimus (Mar 2009)

- Bevacizumab + IFN-α (Jul 2009)
  - Axitinib (Jan 2012)

- Everolimus (Mar 2009)
  - Lenvatinib + Everolimus (May 2016)

- Pazopanib (Oct 2009)
  - Nivolumab (Nov 2015)

- Nivolumab (Nov 2015)
  - Nivolumab + Ipilimumab

- Sunitinib (Jan 2006)
  - Cabozantinib (April 2016)

- Immunotherapy
  - VEGF
  - mTOR

Timeline:
- 1992
- 2005
- 2006
- 2007
- 2009
- 2012
- 2015
- 2016
- 2017
mRCC 1st Line

NCCN Guidelines Version 4.2018
Kidney Cancer

FIRST-LINE THERAPY
(alphabetical by category and preference)

- Clinical trial
- Pazopanib (category 1, preferred)

- Ipilimumab + nivolumab (category 1, preferred for intermediate- and poor-prognosis risk)

- Bevacizumab + interferon alfa-2b (category 1)
- Temsirolimus (category 1 for poor-prognosis risk group, category 2B for selected patients of other risk groups)
- Axitinib
- Cabozantinib (for poor- and intermediate-risk groups)
- High-dose IL-2 for selected patients
- Active surveillance for select, asymptomatic patients

Follow-up (See KID-B)

See Subsequent Therapy for Predominant Clear Cell Histology (KID-4)

Predominant clear cell histology

Relapse or Stage IV and surgically unresectable

Non-clear cell histology

See NCCN Guidelines for Palliative Care

See Systemic Therapy (KID-5)

aSee Risk Models to Direct Treatment (Predictors of Short Survival Used to Select Patients for Temsirolimus) (KID-C).
bSee Risk Models to Direct Treatment (MDC criteria) (KID-C).

cPatients with excellent performance status and normal organ function.


Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
mRCC 2\textsuperscript{nd} Line

NCCN Guidelines Version 4.2018
Kidney Cancer

SUBSEQUENT THERAPY\textsuperscript{m}
(alphabetical by category and preference)

- Clinical trial
- Cabozantinib (category 1, preferred)\textsuperscript{a}
- **Nivolumab (category 1, preferred)\textsuperscript{b}**
- Axitinib (category 1)
- Lenvatinib + everolimus (category 1)
- Everolimus
- Ipilimumab + nivolumab
- Pazopanib
- Sorafenib
- Sunitinib
- Bevacizumab (category 2B)
- High-dose IL-2 for selected patients\textsuperscript{i} (category 2B)
- Temsirolimus (category 2B)
and
Best supportive care.\textsuperscript{i}

See NCCN Guidelines for Palliative Care
CheckMate 025 Study Design

Phase 3, randomized, open-label study of nivolumab vs everolimus in patients with advanced or metastatic clear cell RCC who have received prior anti-angiogenic therapy.¹

Key Inclusion Criteria¹
- Advanced/metastatic clear cell RCC
- ≤3 total prior regimens
- 1 or 2 prior anti-angiogenic therapies
- Progression <6 months before enrollment
- KPS ≥70
- No CNS metastases
- No prior therapy with mTOR inhibitor
- No condition requiring glucocorticoids

Nivolumab
3 mg/kg IV q2w
Until progression,¹ unacceptable toxicity, withdrawal of consent, or end of study

Everolimus
10 mg PO qd

R 1:1
N=821

Start Date: September 2012²
Estimated Trial Completion Date: September 2018²
Primary Completion Date: May 2015²
Status: Ongoing but not recruiting²
Trial Director: Bristol-Myers Squibb²

Primary Endpoint: OS
Secondary Endpoints: ORR, PFS, OS by PD-L1 expression, incidence of AEs

¹Patients were allowed to continue treatment beyond progression if investigator-assessed clinical benefit was achieved and treatment had an acceptable side-effect profile.
AE, adverse event; CNS, central nervous system; IV, intravenous; KPS, Karnofsky performance status; mTOR, mammalian target of rapamycin; ORR, objective response rate; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progression-free survival; PO, oral; qd, once daily; q2w, every 2 weeks;
R, randomized; RCC, renal cell carcinoma.
Overall Survival

CheckMate 025: monotherapy

Median OS, Months (95% CI)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median OS, Months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>25.0 (21.8–NE)</td>
</tr>
<tr>
<td>Everolimus</td>
<td>19.6 (17.6–23.1)</td>
</tr>
</tbody>
</table>

HR (98.5% CI), 0.73 (0.57–0.93)
P=0.002

No. of patients at risk

<table>
<thead>
<tr>
<th>Treatment</th>
<th>0</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>15</th>
<th>18</th>
<th>21</th>
<th>24</th>
<th>27</th>
<th>30</th>
<th>33</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>410</td>
<td>389</td>
<td>359</td>
<td>337</td>
<td>305</td>
<td>275</td>
<td>213</td>
<td>139</td>
<td>73</td>
<td>29</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Everolimus</td>
<td>411</td>
<td>366</td>
<td>324</td>
<td>287</td>
<td>265</td>
<td>241</td>
<td>187</td>
<td>115</td>
<td>61</td>
<td>20</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

Minimum follow-up: 14 months; reported as of June 2015.
CI, confidence interval; HR, hazard ratio; NE, not estimable; OS, overall survival.
CheckMate 025: monotherapy

OS by PD-L1 Expression

**PD-L1 ≥1% (n=181; 24%)**

<table>
<thead>
<tr>
<th></th>
<th>Median OS, Months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>21.8 (16.5–28.1)</td>
</tr>
<tr>
<td>Everolimus</td>
<td>18.8 (11.9–19.9)</td>
</tr>
</tbody>
</table>

**PD-L1 <1% (n=575; 76%)**

<table>
<thead>
<tr>
<th></th>
<th>Median OS, Months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>27.4 (21.4–NE)</td>
</tr>
<tr>
<td>Everolimus</td>
<td>21.2 (17.7–26.2)</td>
</tr>
</tbody>
</table>

Minimum follow-up: 14 months; reported as of June 2015.
CI, confidence interval; NE, not estimable; OS, overall survival; PD-L1, programmed death ligand 1.
CheckMate 214

Phase 3, randomized, open-label trial of nivolumab combined with ipilimumab vs sunitinib monotherapy in treatment-naïve patients with advanced or metastatic clear cell RCC

Key Inclusion Criteria
- Advanced/metastatic clear cell RCC
- No prior systemic therapy for RCC
- Prior adjuvant/neoadjuvant therapy allowed if the agent did not target the VEGF pathway, and recurrence occurred ≥6 months after last dose
- KPS ≥70%
- Available FFPE archival or recent tumor tissue sample
- No prior treatment with VEGF pathway agents or agents targeting T-cell co-stimulation or checkpoint pathways
- No current or history of CNS metastases

Start Date: October 2014
Estimated Trial Completion Date: TBD
Estimated Primary Completion Date: June 2019
Status: Ongoing, not recruiting
Study Director: Bristol-Myers Squibb

CheckMate 214: nivo + ipi, 1L

<table>
<thead>
<tr>
<th>Nivolumab</th>
<th>3 mg/kg IV q3w for 4 doses, then q2w</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunitinib</td>
<td>50 mg PO qd for 4 weeks (6-week cycles)</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>1 mg/kg IV q3w for 4 doses</td>
</tr>
</tbody>
</table>

R 1:1

Primary Outcome Measures: PFS, OS, ORR in intermediate/poor risk patients
Key Secondary Outcome Measures: PFS, OS, and ORR in any-risk patients, incidence of AEs
Select Exploratory Outcome Measures: PFS and OS in favorable risk patients, HRQoL

Please see Clinicaltrials.gov for full inclusion/exclusion criteria.
Patients may continue treatment beyond progression (RECIST 1.1) if investigator-assessed clinical benefit is achieved and treatment is well tolerated.

CheckMate 214: nivo + ipi, 1L

OS: IMDC Intermediate/Poor Risk

12-month OS rates (95% CI), %
- NIVO + IPI: 80 (76–84)
- SUN: 72 (67–76)

18-month OS rates (95% CI), %
- NIVO + IPI: 75 (70–78)
- SUN: 60 (55–65)

No. of patients at risk

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Months</th>
<th>0</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>15</th>
<th>18</th>
<th>21</th>
<th>24</th>
<th>27</th>
<th>30</th>
<th>33</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIVO + IPI</td>
<td>425</td>
<td>425</td>
<td>399</td>
<td>372</td>
<td>348</td>
<td>332</td>
<td>318</td>
<td>300</td>
<td>241</td>
<td>119</td>
<td>44</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>SUN</td>
<td>422</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>
</tbody>
</table>

Based on data cutoff of August 7, 2017.
Median follow-up: 25.2 months.
CI, confidence interval; HR, hazard ratio; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IPI, ipilimumab; NIVO, nivolumab; OS, overall survival; SUN, sunitinib.
## ORR and DOR: IMDC Intermediate/Poor Risk

**Median DOR, Months (95% CI)**

<table>
<thead>
<tr>
<th></th>
<th>Median DOR, Months (95% CI)</th>
<th>Patients With Ongoing Response, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIVO + IPI</td>
<td>NR (21.8–NE)</td>
<td>72</td>
</tr>
<tr>
<td>SUN</td>
<td>18.2 (14.8–NE)</td>
<td>63</td>
</tr>
</tbody>
</table>

**Confirmed ORR**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>N=847</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NIVO + IPI N=425</td>
</tr>
<tr>
<td></td>
<td>SUN N=422</td>
</tr>
<tr>
<td>Confirmed ORR</td>
<td>42 (37–47)</td>
</tr>
<tr>
<td></td>
<td>27 (22–31)</td>
</tr>
</tbody>
</table>

*P<0.001*

**Confirmed BOR**

<table>
<thead>
<tr>
<th>BOR</th>
<th>NIVO + IPI</th>
<th>SUN</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>9b</td>
<td>1b</td>
</tr>
<tr>
<td>PR</td>
<td>32</td>
<td>25</td>
</tr>
<tr>
<td>SD</td>
<td>31</td>
<td>45</td>
</tr>
<tr>
<td>PD</td>
<td>20</td>
<td>17</td>
</tr>
<tr>
<td>Unable to determine/NR</td>
<td>8</td>
<td>12</td>
</tr>
</tbody>
</table>

**Duration of Response (Probability)**

<table>
<thead>
<tr>
<th>Months</th>
<th>No. of patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>NIVO + IPI 177</td>
</tr>
<tr>
<td>6</td>
<td>146</td>
</tr>
<tr>
<td>12</td>
<td>120</td>
</tr>
<tr>
<td>18</td>
<td>55</td>
</tr>
<tr>
<td>24</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>SUN 112</td>
</tr>
<tr>
<td>6</td>
<td>75</td>
</tr>
<tr>
<td>12</td>
<td>52</td>
</tr>
<tr>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td>24</td>
<td>0</td>
</tr>
</tbody>
</table>

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*a*IRRC-assessed ORR and BOR by RECIST v1.1. *b*P<0.001.

Based on data cutoff of August 7, 2017. Median follow-up: 25.2 months.

BOR, best overall response; CI, confidence interval; CR, complete response; DOR, duration of response; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IPI, ipilimumab; IRRC, independent radiologic review committee; NE, not estimable; NIVO, nivolumab; NR, not reported; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; SUN, sunitinib.

## OS Subgroup Analysis: IMDC Intermediate/Poor Risk

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>NIVO + IPI No. of Deaths/Patients</th>
<th>SUN No. of Deaths/Patients</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td>140/425</td>
<td>188/422</td>
<td>0.66 (0.53–0.82)</td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>77/265</td>
<td>118/259</td>
<td>0.66 (0.53–0.82)</td>
</tr>
<tr>
<td>≥65 and &lt;75</td>
<td>46/125</td>
<td>55/133</td>
<td>0.66 (0.53–0.82)</td>
</tr>
<tr>
<td>≥75</td>
<td>17/35</td>
<td>15/30</td>
<td>0.66 (0.53–0.82)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>104/314</td>
<td>130/301</td>
<td>0.71 (0.55–0.92)</td>
</tr>
<tr>
<td>Female</td>
<td>36/111</td>
<td>58/121</td>
<td>0.66 (0.53–0.82)</td>
</tr>
<tr>
<td><strong>Region</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>USA</td>
<td>33/112</td>
<td>43/110</td>
<td>0.64 (0.40–1.00)</td>
</tr>
<tr>
<td>Canada/Europe</td>
<td>51/148</td>
<td>68/147</td>
<td>0.64 (0.40–1.00)</td>
</tr>
<tr>
<td>Rest of the world</td>
<td>56/165</td>
<td>77/165</td>
<td>0.64 (0.40–1.00)</td>
</tr>
<tr>
<td><strong>Baseline IMDC prognostic risk</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>87/314</td>
<td>121/317</td>
<td>0.66 (0.50–0.87)</td>
</tr>
<tr>
<td>Poor</td>
<td>52/102</td>
<td>66/97</td>
<td>0.66 (0.50–0.87)</td>
</tr>
<tr>
<td><strong>Prior nephrectomy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>103/341</td>
<td>127/319</td>
<td>0.69 (0.53–0.89)</td>
</tr>
<tr>
<td>No</td>
<td>37/84</td>
<td>61/103</td>
<td>0.69 (0.53–0.89)</td>
</tr>
<tr>
<td><strong>Baseline PD-L1 expression</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1%</td>
<td>93/284</td>
<td>114/278</td>
<td>0.73 (0.56–0.96)</td>
</tr>
<tr>
<td>≥1%</td>
<td>28/100</td>
<td>57/114</td>
<td>0.73 (0.56–0.96)</td>
</tr>
<tr>
<td>Not reported</td>
<td>19/41</td>
<td>17/30</td>
<td>0.73 (0.56–0.96)</td>
</tr>
</tbody>
</table>

Based on data cutoff of August 7, 2017.
Median follow-up: 25.2 months.
CI, confidence interval; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IPI, ipilimumab; NIVO, nivolumab; PD-L1, programmed death ligand 1; SUN, sunitinib.
Any-grade Treatment-related Adverse Events:
≥15% of Patients in Either Arm (All Treated Patients)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>N+I, % (N = 547)</th>
<th>S, % (N = 535)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>36.9</td>
<td>49.3</td>
</tr>
<tr>
<td>Pruritus</td>
<td>28.2</td>
<td>9.2</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>26.5</td>
<td>12.5</td>
</tr>
<tr>
<td>Rash</td>
<td>21.6</td>
<td>37.8</td>
</tr>
<tr>
<td>Nausea</td>
<td>19.9</td>
<td>25.0</td>
</tr>
<tr>
<td>Increased lipase level</td>
<td>16.5</td>
<td>17.0</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>15.5</td>
<td>24.9</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>13.7</td>
<td>20.6</td>
</tr>
<tr>
<td>Asthenia</td>
<td>13.2</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>10.8</td>
<td>15.5</td>
</tr>
<tr>
<td>Anemia</td>
<td>6.2</td>
<td>15.5</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>5.7</td>
<td>33.5</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>4.2</td>
<td>27.9</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>2.7</td>
<td>17.9</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>2.4</td>
<td>28.4</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.2</td>
<td>40.4</td>
</tr>
<tr>
<td>PPE syndrome</td>
<td>0.9</td>
<td>43.2</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0.4</td>
<td></td>
</tr>
</tbody>
</table>

Based on data cutoff of August 7, 2017.
Median follow-up: 25.2 months.
Included with permission from Tannir NM, et al. Poster presentation at EI KCS 2018.
PPE= palmar-plantar erythrodysesthesia.
Efficacy and Safety of an Attenuated Dose Sunitinib Regimen in Metastatic Renal Cell Carcinoma: Results from a Prospective Registry in Singapore

Hui Shan Tan, Huihua Li, Yu Wen Hong, Chee-Keong Toh, Alvin Wong, Gilberto Lopes, Miah Hiang Tay, Alexandre Chan, Xin Yao, Tiffany Tang, Quan Sing Ng, Ravindran Kanveswaran, Noan Minh Chau, Min-Han Tan

--- Conventional-dose regimen
Median PFS, 6.2 months (95% C.I., 2.5 – 13.8)

--- Attenuated-dose regimen
Median PFS, 7.6 months (95% C.I., 5.0 – 10.0)

HR, 1.18 (95% C.I., 0.71 – 1.98), P = 0.5250

--- Conventional-dose regimen
Median OS\textsubscript{initiation}, 18.3 months (95% C.I. not reached)

--- Attenuated-dose regimen
Median OS\textsubscript{initiation}, 16.5 months (95% C.I., 15.1 – 21.6)

HR, 0.81 (95% C.I., 0.42 – 1.57), P = 0.5391
<table>
<thead>
<tr>
<th>Regimen</th>
<th>GLOBAL</th>
<th>ASIA</th>
<th>ALTERNATIVE REGIMEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regimen</td>
<td>50mg id 4/2</td>
<td>50mg id 4/2</td>
<td>50mg id 4/2</td>
</tr>
<tr>
<td>Sample size</td>
<td>n=750</td>
<td>n=4371</td>
<td>n=1110</td>
</tr>
<tr>
<td>Age at diagnosis, median</td>
<td>62</td>
<td>59</td>
<td>62</td>
</tr>
<tr>
<td>Gender</td>
<td>Male (%)</td>
<td>71</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td>Female (%)</td>
<td>29</td>
<td>25</td>
</tr>
<tr>
<td>Histologic subtype</td>
<td>Clear cell (%)</td>
<td>100</td>
<td>86</td>
</tr>
<tr>
<td></td>
<td>Non clear cell (%)</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>MSKCC</td>
<td>Favorable (%)</td>
<td>38</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>Intermediate (%)</td>
<td>56</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td>Poor (%)</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Response rates</td>
<td>CR (%)</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>PR (%)</td>
<td>44</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>SD (%)</td>
<td>40</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td>PD (%)</td>
<td>7</td>
<td>24</td>
</tr>
<tr>
<td>Survival</td>
<td>OS, months</td>
<td>26.4</td>
<td>18.4</td>
</tr>
<tr>
<td></td>
<td>PFS, months</td>
<td>11</td>
<td>10.9</td>
</tr>
<tr>
<td></td>
<td>Dose reduction (%)</td>
<td>50</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>Dose delay (%)</td>
<td>38</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Dose discontinuation due to AE (%)</td>
<td>19</td>
<td>8</td>
</tr>
</tbody>
</table>

Tan HS et al; Clin Genitourin Cancer. 2014 Nov 18
IO + Anti-VEGF – Is there a rationale for these combinations?

- VEGF signalling decreases dendritic cell (DC) co-stimulatory molecule expression and T cell priming
- VEGF signalling encourages the formation of myeloid-derived suppressor cells (MDSCs)
- VEGF antagonists reverse these effects and promote the formation of potent anti-tumour T cells

Vanneman & Dranoff
Nature Reviews Cancer 2012;12, 237-251
IMmotion151: Phase III atezolizumab + bevacizumab vs. sunitinib

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

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

N = 915

1:1

Atezolizumab 1200 mg IV q3w + Bevacizumab 15 mg/kg IV q3w

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

Coprimary endpoints
- PFS by INV-assessment in PD-L1+
- OS in ITT

Presented By Elizabeth Plimack at 2018 ASCO Annual Meeting
IMmotion151: Primary endpoint #1 met: Progression-Free Survival in PD-L1+

Presented By Elizabeth Plimack at 2018 ASCO Annual Meeting

Median PFS, mo (95% CI)

- Atezo + Bev: 11.2 (8.9, 15.0)
- Sunitinib: 7.7 (6.8, 9.7)

HR: 0.74 (95% CI: 0.57, 0.96)  \( P = 0.02 \)

- PFS assessed by investigators.
- Minimum follow-up, 12 mo. Median of follow-up, 15 mo.

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Months 0</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>15</th>
<th>18</th>
<th>21</th>
<th>24</th>
<th>27</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atezo + Bev</td>
<td>178</td>
<td>137</td>
<td>117</td>
<td>94</td>
<td>79</td>
<td>55</td>
<td>22</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sunitinib</td>
<td>184</td>
<td>135</td>
<td>110</td>
<td>83</td>
<td>64</td>
<td>44</td>
<td>15</td>
<td>7</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>
IMmotion151: Primary endpoint #2, overall survival in intent to treat, awaits next interim analysis

<table>
<thead>
<tr>
<th></th>
<th>PD-L1+ Atezo + Bev (n = 178)</th>
<th>Sunitinib (n = 184)</th>
<th>ITT Atezo + Bev (n = 454)</th>
<th>Sunitinib (n = 461)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, mo (95% CI)</td>
<td>11.2 (8.9, 15.0)</td>
<td>7.7 (6.8, 9.7)</td>
<td>11.2 (9.6, 13.3)</td>
<td>8.4 (7.5, 9.7)</td>
</tr>
<tr>
<td>Stratified HR (95% CI)</td>
<td>0.74 (0.57, 0.96)</td>
<td></td>
<td>0.83 (0.70, 0.97)</td>
<td></td>
</tr>
<tr>
<td>Overall survival, mo Interim analysis (95% CI)</td>
<td>Not reached</td>
<td>23.3 (21.3, NR)</td>
<td>Not reached</td>
<td>Not reached</td>
</tr>
<tr>
<td>Stratified HR (95% CI)</td>
<td>0.68 (0.46, 1.00)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confirmed ORR, % (95% CI)</td>
<td>43% (35, 50)</td>
<td>35% (28, 42)</td>
<td>37% (32, 41)</td>
<td>33% (29, 38)</td>
</tr>
<tr>
<td>Complete response</td>
<td>9%</td>
<td>4%</td>
<td>5%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Presented By Elizabeth Plimack at 2018 ASCO Annual Meeting
Treatment Related Adverse Events in Front Line metastatic ccRCC

USFDA approved standard of care options

Presented By Elizabeth Plimack at 2018 ASCO Annual Meeting
Response Rates in Front Line metastatic ccRCC (all risk groups)

- **Nivolumab** (n=24): 13% (USFDA approved standard option)
  - Choueiri CCR. 2016 PubMed: 27159984

- **Atezolizumab** (n=103): 25%
  - McDermott GU ASCO 2017 Abstract # 431

- **Sunitinib** (n=546): 27%
  - Motzer NEJM 2018 PubMed: 29562145

- **Pazopanib** (n=557): 31%
  - Motzer NEJM 2013 PubMed: 23964934

- **Bevacizumab Atezolizumab** (n=454): 37%
  - Escudier ASCO 2018 Abstract # 4511

- **Pembrolizumab** (n=110): 38%
  - McDermott ASCO 2018 Abstract # 4500

- **Ipilimumab Nivolumab** (n=550): 39%
  - Motzer NEJM 2018 PubMed: 29562145

- **Axitinib Avelumab** (n=55): 68%
  - Choueiri Lancet Onc 2018 PubMed: 29539687

- **Axitinib Pembrolizumab** (n=52): 73%
  - Atkins Lancet Onc 2018 PubMed: 29458687

Presented By Elizabeth Plimack at 2018 ASCO Annual Meeting
Pembrolizumab/Axitinib Improves Survival in Frontline RCC

OncLive Staff
Published: Thursday, Oct 18, 2018

Combining the PD-1 inhibitor pembrolizumab (Keytruda) with the VEGF inhibitor axitinib (Inlyta) significantly improved survival versus sunitinib (Sutent) as a first-line treatment for patients with advanced or metastatic renal cell carcinoma (RCC), according to findings from the phase III KEYNOTE-426 trial.¹

Merck (MSD), the manufacturer of pembrolizumab, announced in a press release that the study had met the coprimary endpoints of significant improvement in overall survival (OS) and progression-free survival (PFS), as well as the secondary endpoint of
## 1\textsuperscript{st} line Phase III trials of combination IO based therapies in mRCC

<table>
<thead>
<tr>
<th>Therapeutic target</th>
<th>Control arm</th>
<th>Experimental arm(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-1 and CTLA-4</td>
<td>Sunitinib</td>
<td>(Nivolumab + Ipilimumab) x 4 →                                      Nivolumab</td>
</tr>
<tr>
<td>PD1 and IDO-1</td>
<td>Sunitinib or Pazopanib</td>
<td>Pembrolizumab + Epacadostat</td>
</tr>
<tr>
<td>PD-1 and VEGF</td>
<td>Sunitinib</td>
<td>Bevacizumab + Atezolizumab</td>
</tr>
<tr>
<td>PD-L1 and VEGF</td>
<td>Sunitinib</td>
<td>Axitinib + Avelumab</td>
</tr>
<tr>
<td>PD-L1 and VEGF</td>
<td>Sunitinib</td>
<td>Axitinib + Pembrolizumab</td>
</tr>
<tr>
<td>VEGF/FGF and (PD1 or mTOR)</td>
<td>Sunitinib</td>
<td>Lenvatinib + Pembrolizumab OR Lenvatinib + Everolimus</td>
</tr>
<tr>
<td>Vaccine (DC+autologous tumor)</td>
<td>Sunitinib</td>
<td>Sunitinib + AGS-003 (Rocapuldencel-T)</td>
</tr>
</tbody>
</table>

Modified from G. Sonpavde
Progress in metastatic RCC

US FDA APPROVALS

- Sorafenib Dec 20, 2005
- Sunitinib Jan 26, 2006
- Temsirolimus May 30, 2007
- Everolimus Mar 30, 2009
- Bevacizumab + IFN Jul 31, 2009
- Pazopanib Oct 19, 2009
- Axitinib Jan 27, 2012
- Nivolumab Nov 23, 2015
- Cabozantinib Apr 25, 2016
- Lenvatinib May 13, 2016
- Ipilimumab Apr 16, 2018
- Nivolumab

Percent of patients alive 2 yrs after starting first line therapy

- Sunitinib, 54%
- Bevacizumab + IFN, 50%
- Pazopanib, 58%
- Sunitinib, 58%
- Cabozantinib, 55%
- Ipi + Nivo, 71%
- Axi + Pembro, 87%

PubMed PMID:
- 23598172
- 26482279
- 23598172
- 20549832
- 29550566
- 29562145
- 28438657

Presented By Elizabeth Plimack at 2018 ASCO Annual Meeting
Summary

1) 1st line treatment of mRCC:
   **Favourable risk**- Sunitinib or Pazopanib
   **Intermediate/ Poor risk**: Ipi/Nivo or Cabozantinib

2) To look out for combination data coming out soon

3) Cost will be a major factor in determining choice/accessibility (value based care)
Outline

• Immunotherapy in mRCC

• Immunotherapy in mUC

• Future Directions

• Summary
Bladder Cancer- highly mutagenic
Evolution of systemic therapy for urothelial cancer till 2016

Evolution of systemic therapy for urothelial cancer to 2018

# Checkpoint Inhibitors Approved for Use in Urothelial Carcinoma

7 US FDA Approvals May 2016-May 2017
5 EAU approvals

<table>
<thead>
<tr>
<th>Setting</th>
<th>Antibody</th>
<th>Approval Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st line (cisplatin- ineligible)</td>
<td>Atezolizumab</td>
<td>• Accelerated approval granted in April 2017</td>
</tr>
<tr>
<td></td>
<td>Pembrolizumab</td>
<td>• Accelerated approval granted in May 2017</td>
</tr>
<tr>
<td>Platinum-pretreated</td>
<td>Atezolizumab</td>
<td>• Accelerated approval granted in May 2016.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• In May 2017, the subsequent phase 3 IMvigor211 trial did not meet primary endpoint of overall survival</td>
</tr>
<tr>
<td></td>
<td>Nivolumab</td>
<td>• Accelerated approval granted in February 2017</td>
</tr>
<tr>
<td></td>
<td>Durvalumab</td>
<td>• Accelerated approval granted in May 2017</td>
</tr>
<tr>
<td></td>
<td>Avelumab</td>
<td>• Accelerated approval granted in May 2017</td>
</tr>
<tr>
<td></td>
<td>Pembrolizumab</td>
<td>• Full approval granted in May 2017</td>
</tr>
</tbody>
</table>

Courtesy of J.Bellmunt
IMvigor 210, a Phase II trial of Atezolizumab (MPDL3280A) in Platinum-treated Locally Advanced or Metastatic Urothelial Carcinoma (mUC)


¹Kimmel Cancer Center, Thomas Jefferson University Hospital, Philadelphia, PA, USA; ²Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, USA; ³Netherlands Cancer Institute, Amsterdam, Netherlands; ⁴Division of Hematology/Oncology, University of Virginia, Charlottesville VA USA; ⁵Gustave Roussy, Villejuif, France; ⁶Urologische Klinik und Poliklinik, Technische Universität München, Munich, Germany; ⁷US Oncology Research/Comprehensive Cancer Centers of Nevada, Las Vegas, NV, USA; ⁸Clinica Universidad de Navarra, Pamplona, Spain; ⁹Norton Cancer Institute, Louisville, KY, USA; ¹⁰USL8 Ospedale San Donato, Arezzo, Italy; ¹¹University of Washington and Seattle Cancer Care Alliance, Seattle, WA, USA; ¹²Seidman Cancer Center, Case Western Reserve University, Cleveland, OH, USA; ¹³Bladder Cancer Center, Dana-Farber/Brigham and Women’s Cancer Center, Harvard Medical School, Boston, MA, USA; ¹⁴USC Norris Comprehensive Cancer Center, Los Angeles, CA, USA; ¹⁵Yale Cancer Center, New Haven, CT, USA; ¹⁶University of Liverpool, Clatterbridge Cancer Centre, Liverpool, UK; ¹⁷Genentech, Inc, South San Francisco, CA, USA; ¹⁸Memorial Sloan Kettering Cancer Center, New York, NY, USA.
Phase II IMvigor 210 Study of Atezolizumab in mUC

- Co-primary endpoints:  
  (1) ORR per confirmed RECIST v1.1 and central IRF  
  (2) ORR per investigator-assessed modified RECIST  
- Key secondary endpoints: DOR, PFS, OS, safety

*IC, tumor-infiltrating immune cell; IRF, independent review facility.  
*Patients and investigators blinded to PD-L1 IHC status. Trial enrolled an all-comer population with a minimum of 100 IC2/3 patients.  
Trial Identifier: NCT02108652

Presented By Jean Hoffman-Censits at Genitourinary Cancers Symposium 2016
**IMvigor 210: Responses to Atezolizumab**

<table>
<thead>
<tr>
<th></th>
<th>IC2/3 (n = 100)</th>
<th>IC1/2/3 (n = 207)</th>
<th>All (N = 310)</th>
<th>IC1 (n = 107)</th>
<th>IC0 (n = 103)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (95% CI) per confirmed IRF RECIST v1.1</td>
<td>26% (18, 36)</td>
<td>18% (13, 24)</td>
<td>15% (11, 19)</td>
<td>10% (5, 18)</td>
<td>8% (3, 15)</td>
</tr>
<tr>
<td>ORR (95% CI) per investigator mRECIST</td>
<td>27% (19, 37)</td>
<td>22% (16, 28)</td>
<td>19% (15, 24)</td>
<td>17% (10, 25)</td>
<td>13% (7, 21)</td>
</tr>
<tr>
<td>Complete response (CR) per confirmed IRF RECIST v1.1</td>
<td>11%</td>
<td>6%</td>
<td>5%</td>
<td>2%</td>
<td>2%</td>
</tr>
</tbody>
</table>

- Higher ORR was associated with higher PD-L1 IHC status, but responses were seen in all PD-L1 subgroups

Objective response evaluable population: all treated patients had measurable disease at baseline per investigator-assessed RECIST v1.1.
Data cutoff: September 14, 2015.
IMVIGOR 210 Cohort 1

Efficacy

Overall Survival (Median and Landmark 12-Month OS)

mOS (95% CI): 14.8 mo (10.1, NE)
12-mo OS (95% CI): 57% (48, 66)

Overall Survival, %

12-mo OS rate:
57% (48, 66)

Time, months
0 2 4 6 8 10 12 14 16 18 20

N = 119
+ censored event

# at Risk:
All 119 101 89 78 71 64 52 33 16 7 1
Immune checkpoint inhibitors as first-line in cisplatin-ineligible patients

<table>
<thead>
<tr>
<th></th>
<th>Atezolizumab&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Pembrolizumab&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase</strong></td>
<td>Phase II (IMvigor Cohort 1)</td>
<td>Phase II (Keynote-052)</td>
</tr>
<tr>
<td><strong>Number of patients</strong></td>
<td>119</td>
<td>370</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>1200 mg every 3 weeks</td>
<td>200 mg every 3 weeks</td>
</tr>
<tr>
<td><strong>ORR</strong></td>
<td>23% (9% CR)</td>
<td>29% (7% CR)</td>
</tr>
<tr>
<td><strong>Duration of response</strong></td>
<td>70% of responses ongoing at 17.2 months</td>
<td>82% of responses ongoing at ≥ 6 months</td>
</tr>
<tr>
<td><strong>Median OS</strong></td>
<td>15.9 months</td>
<td>11.5 months</td>
</tr>
<tr>
<td><strong>Median PFS</strong></td>
<td>2.7 months</td>
<td>2.0 months</td>
</tr>
<tr>
<td><strong>Rate of Grade 3/4 treatment-related AEs</strong></td>
<td>16%</td>
<td>19%</td>
</tr>
</tbody>
</table>

Opposite results in the cis-ineligible 1st line single arm trials

**Vuky # 4524**

In KN052 – Cisplatin ineligible front line **pembrolizumab**, low PDL1 (CPS <10) patients were 74% of the study population and had worse median OS.

**Balar # 4523**

In contrast, in IMvigor210 – Cisplatin ineligible front line **atezolizumab** - low PDL1 (IC0/1) patients were 70% of the study population and had similar to slightly better median OS.

Table 3. Overall Survival by Subgroups

<table>
<thead>
<tr>
<th>Response</th>
<th>N</th>
<th>Events, n(%)</th>
<th>Median OS (95% CI), mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-L1 subgroup</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD-L1 CPS &lt;10</td>
<td>251</td>
<td>186 (74)</td>
<td>10.0 (7.8-11.6)</td>
</tr>
<tr>
<td>PD-L1 CPS ≥10</td>
<td>110</td>
<td>57 (52)</td>
<td>10.5 (12.2 to NR)</td>
</tr>
</tbody>
</table>

Balar AV, et al. J Clin Oncol 36, 2018 (suppl; abstr 4523)
## Immune checkpoint inhibitors in platinum-refractory setting

<table>
<thead>
<tr>
<th></th>
<th>Atezolizumab&lt;sup&gt;1,6&lt;/sup&gt;</th>
<th>Nivolumab&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Pembrolizumab&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Avelumab&lt;sup&gt;4&lt;/sup&gt;</th>
<th>Durvalumab&lt;sup&gt;5&lt;/sup&gt;</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&lt;sup&gt;1&lt;/sup&gt; 467&lt;sup&gt;6&lt;/sup&gt;</td>
<td>265</td>
<td>270</td>
<td>249 (242 pts ≥12 months follow-up)</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%; IC2/3 23%</td>
<td>19.6%</td>
<td>21.1%</td>
<td>16.1%</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&lt;sup&gt;6&lt;/sup&gt;</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%/20%&lt;sup&gt;6&lt;/sup&gt;</td>
<td>18%</td>
<td>13.5% (15% G3–5)</td>
<td>10.8% G3–5</td>
<td>6.8%</td>
</tr>
</tbody>
</table>

SECOND LINE Phase III

**KEYNOTE-045** Study Design (NCT02256436)

- Urothelial cancer
- Progression or recurrence of urothelial cancer following a first-line platinum-containing regimen.
- No more than 2 prior lines of systemic chemotherapy.

<table>
<thead>
<tr>
<th>Randomization</th>
<th>Pembrolizumab</th>
<th>Primary end points</th>
<th>OS &amp; PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 542 patients</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Estimated timelines:
- Estimated completion: Sept 2016 (Early termination)

<table>
<thead>
<tr>
<th>SOC: Paclitaxel, Docetaxel or Vinflunine</th>
<th>Secondary end points</th>
<th>ORR, Safety</th>
</tr>
</thead>
</table>

**IMvigor211** Study Design (NCT02302807)

- Urothelial cancer
- Progression or recurrence of urothelial cancer following a first-line platinum-containing regimen.

<table>
<thead>
<tr>
<th>Randomization</th>
<th>Atezolizumab</th>
<th>Primary end points</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 932 patients</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Estimated timelines:
- Estimated completion: Nov 2017

<table>
<thead>
<tr>
<th>SOC: Docetaxel, Paclitaxel or Vinflunine</th>
<th>Secondary end points</th>
<th>ORR, PFS, DOR, Safety</th>
</tr>
</thead>
</table>

Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma

Joaquim Bellmunt, M.D., Ph.D., Ronald de Wit, M.D., Ph.D., David J. Vaughn, M.D., Yves Fradet, M.D., Jae-Lyun Lee, M.D., Ph.D., Lawrence Fong, M.D., Nicholas J. Vogelzang, M.D., Miguel A. Climent, M.D., Daniel P. Petrylak, M.D., Toni K. Choueiri, M.D., Andrea Necchi, M.D., Winald Gerritsen, M.D., Ph.D., Howard Gurney, M.D., David I. Quinn, M.D., Ph.D., Stéphane Cunin, M.D., Ph.D., Cora N. Sternberg, M.D., Yabing Mai, Ph.D., Christian H. Poehlein, M.D., Rodolfo F. Perini, M.D., and Dean F. Bajorin, M.D., for the KEYNOTE-045 Investigators

KEYNOTE-045: Study Design

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

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

**Key End Points**
- Primary: OS and PFS in total and PD-L1 CPS ≥10% populations
- Secondary: OR and DOR in total and PD-L1 CPS ≥10% populations; safety in total population

**Pembrolizumab**
- 200 mg IV Q3W
- For 2 years

**Randomization (1:1)**
- N=54
- n=270

**Treatments**
- Paclitaxel 175 g/m² Q3W
- Docetaxel 75 mg/m² Q3W
- Vinflunine 320 mg/m² Q3W

**N=272**

---

CPS = combined positive score; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; IV = intravenous; OS = overall survival; PD = progressive disease; PD-L1 = programmed death ligand 1; PFS = progression-free survival; PS = performance status; Q3W = every 3 weeks; R = randomization.

KEYNOTE-045: OVERALL SURVIVAL

Overall Survival: Total

<table>
<thead>
<tr>
<th>Events, n</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro</td>
<td>155</td>
<td>0.73 (0.59-0.91)</td>
</tr>
<tr>
<td>Chemo</td>
<td>179</td>
<td></td>
</tr>
</tbody>
</table>

No. at risk

Data cutoff date: Sep 7, 2016

Overall Survival: CPS ≥10%

<table>
<thead>
<tr>
<th>Events, n</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro</td>
<td>44</td>
<td>0.57 (0.37-0.88)</td>
</tr>
<tr>
<td>Chemo</td>
<td>60</td>
<td></td>
</tr>
</tbody>
</table>

No. at risk

Data cutoff date: Sep 7, 2016

Key Eligibility Criteria
- mUC with progression during or following platinum-based chemotherapy
  - ≤ 2 prior lines of therapy
- Measurable disease per RECIST v1.1
- ECOG PS 0-1
- Evaluable sample for PD-L1 testing
- TCC histology as primary component
  \(N = 931\)

Primary endpoint
- OS, tested hierarchically in pre-specified populations

Stratification Factors
- No. of risk factors\(^b\) (0 vs. 1/2/3)
- Liver metastases (yes vs. no)
- PD-L1 status (0/1 vs. 2/3)
- Chemotherapy (vinflunine vs. taxanes)

Additional endpoints
- Efficacy: RECIST v1.1 ORR, PFS and DOR\(^c\)
- Safety
- PROs: EORTC QLQ-C30

DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organisation for Research and Treatment of Cancer; PRO, patient-reported outcome; q3w, every three weeks; RECIST, Response Evaluation Criteria In Solid Tumors; TCC, transitional cell carcinoma. \(^a\)ClinicalTrials.gov, NCT02302807. \(^b\)Defined by time from prior chemotherapy < 3 mo, ECOG performance status > 0 and hemoglobin < 10 g/dL. \(^c\)Confirmed response was not required for secondary efficacy endpoints. This analysis reports exploratory confirmed responses.

Powles T, et al. EAS 2017, IMvigor211.
Atezolizumab

IMvigor 211

OS in PD-L1 IC2/3.

<table>
<thead>
<tr>
<th>Events/Patients</th>
<th>Median OS (95% CI)</th>
<th>12-mo OS Rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atezolizumab</td>
<td>72/116</td>
<td>11.1 mo (8.6, 15.5)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>88/118</td>
<td>10.6 mo (8.4, 12.2)</td>
</tr>
</tbody>
</table>

OS in PD-L1 IC 1/2/3.

<table>
<thead>
<tr>
<th>Events/Patients</th>
<th>Median OS (95% CI)</th>
<th>12-mo OS Rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atezolizumab</td>
<td>220/316</td>
<td>8.9 mo (8.2, 10.9)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>232/309</td>
<td>8.2 mo (7.4, 9.5)</td>
</tr>
</tbody>
</table>

Imvigor 211: OS for ITT

Where Do We Go from Here?
Select Ongoing/ Completed Trials in Bladder Cancer

Non-Muscle Invasive

Muscle Invasive

Treatment naïve Metastatic

Pretreated Metastatic

KEYNOTE-057 (Ph 2):
• Pembrolizumab in BCG unresponsive NMIBC

NCT02792192 (Ph 1/2):
• Atezolizumab ± BCG in high risk NMIBC

CheckMate 274 (Ph 3):
• Nivolumab vs placebo postsurgery MIBC

IMvigor 010 (Ph 3):
• Atezolizumab vs observation postsurgery PD-L1+ MIBC

DANUBE (Ph 3):
• Durvalumab ± Tremelimumab vs chemo Tx-naïve, unresectable, urothelial carcinoma

KEYNOTE-052 (Ph 2):
• Pembrolizumab Tx-naïve, cisplatin ineligible, locally advanced mUC

KEYNOTE-361 (Ph 3):
• Pembrolizumab ± chemo vs chemo in Tx-naïve advanced or mUC

IMvigor 130 (Ph 3):
• Atezolizumab gem-cis vs gem-cis in untreated advanced or mUC

JAVELIN Bladder 100 (Ph 3):
• Avelumab as maintenance vs BSC for locally advanced mUC

CheckMate 275 (Ph 2):
• Nivolumab for locally advanced or mUC after Pt failure

IMvigor 211 (Ph 3):
• Atezolizumab vs chemo in locally adv or mUC, after Pt failure

KEYNOTE-045 (Ph 3):
• Pembrolizumab vs chemo in locally adv or mUC, after Pt failure

Phase III trials on the horizon

Pembrolizumab in combination with platinum-containing regimen in first line treatment of advanced bladder cancer

Eligibility
- 1L urothelial carcinoma
- Archival or Fresh Biopsy
- Measurable Disease
- ECOG Status 0, 1 and 2
- Hemoglobin >9 g/dL

Randomization 1:1:1

Primary endpoint
- PFS + OS

Secondary endpoint
- DOR
- DCR
- Safety

Exploratory endpoints
- PKPD
- Biomarkers and genomics
- PRO

Target enrollment: 990
First line Phase III Study of Nivolumab in Combination With Ipilimumab Compared to the Standard of Care Chemotherapy in Treatment of Patients With Untreated Inoperable or Metastatic Urothelial Cancer (CheckMate901)
Ineligible for any Platinum

Cisplatin Ineligible

PD-L1 (IHC)

Low

Carboplatin-based chemotherapy

High

Pembrolizumab/atezolizumab

Pembrolizumab/atezolizumab?
<table>
<thead>
<tr>
<th>Disease state</th>
<th>Context</th>
<th>Level 1 evidence</th>
<th>Standard Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastatic, no prior chemotherapy</td>
<td>Cisplatin-eligible</td>
<td>Cisplatin-based combination chemotherapy</td>
<td>Atezolizumab *</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pembrolizumab *</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Atezolizumab *</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pembrolizumab Nivolumab Durvalumab Avelumab</td>
</tr>
<tr>
<td>Metastatic, prior platinum chemotherapy or relapse within 1 year of perioperative cisplatin-based therapy</td>
<td></td>
<td>Pembrolizumab</td>
<td></td>
</tr>
<tr>
<td>Metastatic, prior immunotherapy</td>
<td></td>
<td></td>
<td>Taxane Vinflunine (EU)</td>
</tr>
</tbody>
</table>

- Only high PDL1 expressors
- Red highlight – HSA Approval
Summary

- Cisplatin eligible patients should still receive cisplatin based combination therapy (standard of care)

- Pembro or Atezo can be used for cisplatin ineligible patients but only the high PDL1 expressors as defined by the latest studies. It is also an option for patients who would otherwise be unfit for any chemotherapy

- Challenges remain with regards to access to the companion diagnostics

- Await the phase III data for the all the combination IO-chemo studies which may likely be practice changing
THANK YOU

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National Cancer Centre Singapore • National Dental Centre Singapore • National Heart Centre Singapore • National Neuroscience Institute • Singapore National Eye Centre
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