Immunotherapy in the Management of Advanced Urothelial Cancer

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Urothelial (Bladder and Upper Urinary Tract) Cancer

- 4th most common cancer in men and 12th most common cancer in women in 2015
- 74,000 new cases and 16,000 deaths in 2015
- Recurrence and routine surveillance/treatment make bladder cancer most expensive malignancy to treat from diagnosis to death ($187,241/patient in 2001)
- No new FDA-approved drugs for urothelial cancer since BCG

Siegel et al. CA Cancer J Clin 2015
Urothelial Cancer
Gemcitabine/Cisplatin vs. MVAC
Overall Survival

GC: Med = 13.8 (12.3 - 15.8)
MVAC: Med = 14.8 (13.2 - 16.8)
HR: 1.02 (0.82 - 1.32)
LR: p = 0.746
W: p = 0.908
Phase III Trial of Neoadjuvant MVAC + Cystectomy to Cystectomy Alone - INT 0080
Survival

# Systemic Therapy for Bladder Cancer Pre-2016

<table>
<thead>
<tr>
<th>Non-Muscle Invasive</th>
<th>Neoadjuvant Adjuvant</th>
<th>1st Line Metastatic</th>
<th>Next Line Metastatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>No systemic therapy</td>
<td>Gem + Cisplatin or A-MVAC (Cisplatin)</td>
<td>Gem + Cisplatin A-MVAC (Cisplatin) or Gem + Carbo</td>
<td>Paclitaxel/Docetaxel + Vinflunine*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ORR: 12% Median OS 7 mo. 1 year OS 26%*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Carbo + Docetaxel + Vinflunine*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ORR: 50-60% Median OS 15 mo. 1 year OS 60%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Carboplatin ORR 36% Median OS 9 mo. 1 year OS 37%</td>
</tr>
</tbody>
</table>


c/o B. Plimack
Realizing the Potential of Immunotherapy in Cancer

<table>
<thead>
<tr>
<th>Disease</th>
<th>Year</th>
<th>FDA approval</th>
<th>EMA approval</th>
<th>Drug 1</th>
<th>Drug 2</th>
<th>Drug 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma</td>
<td>1992</td>
<td>IFN</td>
<td>IL-2</td>
<td>pegIFN</td>
<td>Ipilimumab</td>
<td>Nivolumab</td>
</tr>
<tr>
<td>RCC</td>
<td>1998</td>
<td>IL-2</td>
<td></td>
<td></td>
<td></td>
<td>Nivolumab</td>
</tr>
<tr>
<td>NSCLC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Nivolumab</td>
</tr>
<tr>
<td>UC</td>
<td></td>
<td></td>
<td></td>
<td>BCG</td>
<td></td>
<td>Atezolizumab</td>
</tr>
<tr>
<td>cHL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Nivolumab</td>
</tr>
<tr>
<td>Prostate</td>
<td></td>
<td></td>
<td></td>
<td>Sipuleucel-T</td>
<td></td>
<td>Nivolumab</td>
</tr>
<tr>
<td>HNSCC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pembrolizumab</td>
</tr>
</tbody>
</table>

Slide adapted from Aurélien Marabelle. ESMO 2016.
Rationale for Immunotherapy in Urothelial Carcinoma
Topics to Be Covered

- Bladder cancer immunotherapy
  - Historic rationale
  - Anti–PD-1/PD-L1 approaches
  - Predictive biomarkers
  - Future combinations/strategies
Immunotherapy for Urothelial Cell Carcinoma
Not a New Idea: Bacillus Calmette-Guérin

- Exact MOA of BCG unclear; however, 3 key steps recognized:
  - Internalization of BCG into urothelial cells and cancer cells
  - Induction of immune reaction via cytokine release with increased APC
  - Induction of antitumor effects

- Limitations of BCG
  - Limited efficacy (best in CIS) with ~ 50% recurrence after induction\textsuperscript{[1,2]} and fewer effects on reinduction
  - Adverse events common although usually mild
  - Role for combination with interferon not definite

Maintenance BCG Immunotherapy in Non-Muscle Invasive Urothelial Cell Carcinoma

- After BCG induction, pts received maintenance BCG (n = 192) or observation (n = 192)
  - BCG maintenance: weekly for 3 wks at 3 mos, 6 mos, and then every 6 mos for 3 yrs

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**RFS**

- Events: Maintenance = 108, No Maintenance = 142
- Median RFS, mos: Maintenance = 77, No Maintenance = 36

**OS**

- Deaths: Maintenance = 81, No Maintenance = 93
- Median OS, mos: Maintenance = NR, No Maintenance = 120

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Patient Case

- A 79-yr-old white male is diagnosed with T3N1 urothelial cancer
- 1 year later, he is found to have recurrence with retroperitoneal adenopathy and pulmonary nodules
  - He is treated with gemcitabine and cisplatin for 4 cycles with resolution of pulmonary nodules
- 7 months later, he is found to have recurrent pulmonary nodules
- Assessment of PD-L1 expression was not performed
Bladder Cancer Has High Mutational Burden Compared With Other Tumors

Somatic Mutation Prevalence (Number Mutations per Megabase)

Change in Approach to Immunotherapy in RCC

Immunosurveillance
- Cancer cells
- Macrophages
- Myeloid-derived Suppressor Cells
- Dendritic cells
- Tregs

Immunotolerance
- Natural Killer Cells
- CD4+ T-cells
- CD8+ T-cells
- Effector phase

IL-2, IFN

PD-1/PD-L1, CTLA-4 Inhibition

Slide adapted from Aurélien Marabelle. ESMO 2016.
**PD-1 Pathway and Immune Surveillance**

**Lymph Node**

**Priming Phase**
- Dendritic cell
- T-cell
- Activating signal
  - MHC
  - TCR
- Inhibitory signal blocked by antibody binding
  - B7
  - CTLA-4

**Tumor Microenvironment**

**Effector Phase**
- T-cell
- Tumor
- Activating signal
  - MHC
  - TCR
- Negative regulation blocked by antibody binding
  - PD-L1
  - PD-L2

## PRINCIPLES OF SYSTEMIC THERAPY

### First-line chemotherapy for locally advanced or metastatic disease

<table>
<thead>
<tr>
<th>Cisplatin eligible</th>
<th>Standard regimens</th>
<th>Alternate regimens for select patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gemcitabine and cisplatin (category 1)</td>
<td>DDMVAC with growth factor support (category 1)</td>
</tr>
<tr>
<td><strong>Cisplatin ineligible:</strong> poor kidney function or poor PS</td>
<td>Gemcitabine and carboplatin</td>
<td>Gemcitabine and paclitaxel</td>
</tr>
<tr>
<td><strong>Cisplatin ineligible:</strong> due to hearing/neuropathy but good kidney function and good PS</td>
<td>Ifosfamide, doxorubicin, and gemcitabine</td>
<td></td>
</tr>
</tbody>
</table>

### Subsequent systemic therapy for locally advanced or metastatic disease

- Participation in clinical trials of new agents is recommended.

<table>
<thead>
<tr>
<th>Standard regimens</th>
<th>Alternate regimens for select patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atezolizumab</td>
<td>Nab-paclitaxel</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>Ifosfamide</td>
</tr>
<tr>
<td>Paclitaxel or docetaxel</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>Ifosfamide, doxorubicin, and gemcitabine</td>
</tr>
<tr>
<td>Pemetrexed</td>
<td>Gemcitabine and paclitaxel</td>
</tr>
<tr>
<td></td>
<td>Gemcitabine and cisplatin</td>
</tr>
<tr>
<td></td>
<td>DDMVAC</td>
</tr>
</tbody>
</table>

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.

FDA approved Feb 2, 2017
**IMvigor 210: Atezolizumab for Advanced Urothelial Cancer**

- Single-arm phase II study with 2 cohorts\(^1\)

- Pts with inoperable advanced or metastatic UC, evaluable tumor tissue for PD-L1 testing, CrCl ≥ 30 mL/min, ECOG PS 0/1; for Cohort 2, any number of prior therapies allowed (N = 429)

- **Cohort 1**\(^2\)
  
  Previously untreated, cisplatin ineligible (n = 119)

- **Cohort 2**\(^3,4\)
  
  Prior platinum treatment (n = 310)

- **Atezolizumab**
  
  1200 mg IV Q3W until PD

- **Atezolizumab**
  
  1200 mg IV Q3W until loss of benefit

- Coprimary endpoints: confirmed ORR by RECIST v1.1 (per central review), ORR by immune-modified RECIST (per investigator)

- Secondary endpoints: DoR, PFS, OS, safety

- Exploratory endpoints: biomarkers

IMvigor 210: PD-L1 Immune Cell Expression by IHC

IHC Status of Treated Patients in IMvigor 210 Study

- PD-L1 ≥ 5% (IC2/3)
- PD-L1 ≥ 1% but < 5% (IC1)
- PD-L1 < 1% (IC0)

Images at 10 x magnification.


- PD-L1 expression prospectively evaluated and categorized into 3 infiltrating immune cell (IC) populations based on IHC scoring levels
## IMvigor 210: Baseline Characteristics and Previous Therapy

<table>
<thead>
<tr>
<th>Characteristic, %</th>
<th>Patients (N = 310)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>78</td>
</tr>
<tr>
<td>IC PD-L1 status</td>
<td></td>
</tr>
<tr>
<td>IC2/3</td>
<td>32</td>
</tr>
<tr>
<td>IC1</td>
<td>35</td>
</tr>
<tr>
<td>IC0</td>
<td>33</td>
</tr>
<tr>
<td>Bladder primary tumor site</td>
<td>74</td>
</tr>
<tr>
<td>Metastatic sites</td>
<td></td>
</tr>
<tr>
<td>Visceral*</td>
<td>78</td>
</tr>
<tr>
<td>Liver</td>
<td>31</td>
</tr>
<tr>
<td>Lymph node only</td>
<td>14</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td></td>
</tr>
<tr>
<td>&lt; 60 mL/min</td>
<td>36</td>
</tr>
<tr>
<td>ECOG PS 1</td>
<td>62</td>
</tr>
<tr>
<td>Prior cystectomy or nephroureterectomy</td>
<td>66</td>
</tr>
<tr>
<td>Prior regimens in metastatic setting</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>19</td>
</tr>
<tr>
<td>1</td>
<td>39</td>
</tr>
<tr>
<td>2</td>
<td>21</td>
</tr>
<tr>
<td>≥ 3</td>
<td>21</td>
</tr>
</tbody>
</table>

*Liver, bone, non-lymph node, or soft tissue metastasis.

IMvigor 210: Duration of Atezolizumab Treatment and DoR

- ORR: 16%
- Median DoR not yet reached in all pts at median follow-up of 21.0 mos
- 65% (32 of 49 responding pts per IRF RECIST v1.1) with ongoing responses at data cutoff

*Pt deceased/timing not implied. †No PD or death.
**IMvigor 210: Updated OS**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>IC0/1 (n = 210)</th>
<th>IC2/3 (n = 100)</th>
<th>All Pts (N = 310)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, mos</td>
<td>6.7 (5.4-8.0)</td>
<td>11.9 (9.0-NE)</td>
<td>7.9 (6.7-9.3)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12-mo OS rate, %</td>
<td>31 (24-37)</td>
<td>50 (40-60)</td>
<td>37 (31-42)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IMvigor 210: Safety

- Median treatment duration: 12 wks (range: 0-66)
- Median number of doses: 5 (range: 1-23)
- No treatment-related deaths
- AE profiles consistent across all PD-L1 IC score populations

<table>
<thead>
<tr>
<th>AE, % (n = 310)</th>
<th>Any Cause</th>
<th>Treatment Related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>97</td>
<td>69</td>
</tr>
<tr>
<td>Serious AE</td>
<td>48</td>
<td>11</td>
</tr>
<tr>
<td>Grade 3/4</td>
<td>55</td>
<td>16</td>
</tr>
<tr>
<td>Grade 5</td>
<td>1*</td>
<td>0</td>
</tr>
<tr>
<td>Immune-mediated AE</td>
<td>7</td>
<td>--</td>
</tr>
<tr>
<td>AE leading to withdrawal</td>
<td>4</td>
<td>N/A</td>
</tr>
<tr>
<td>AE leading to dose modification/disruption</td>
<td>30</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Data cutoff: September 14, 2015.
*Cerebral hemorrhage, pulmonary sepsis, subileus/intestinal occlusion, n = 1 each.
Checkmate-275: Study Design

- A multicenter, single arm phase II trial

Pts with measurable metastatic or locally advanced urothelial carcinoma after recurrence or progression following ≥ 1 platinum-based chemotherapy; ECOG PS 0 or 1; evaluable tumor tissue for biomarker testing (N = 270)

**Nivolumab**
3 mg/kg Q2W (N = 270)

Treated PD and clinical deterioration, unacceptable AE, or protocol-defined decision*

- Primary endpoints: ORR in all pts, ORR in pts with PD-L1 ≥ 5% or ≥ 1%
- Secondary endpoints: PFS, OS, TTR, DoR, safety, QoL

*Pts allowed to continue treatment beyond initial radiographic progression if well tolerated and clinical benefit was noted.
## Checkmate-275: Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic, %</th>
<th>Nivolumab (N = 270)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, yrs (range)</td>
<td>66 (38-90)</td>
</tr>
<tr>
<td>Age ≤ 65</td>
<td>45</td>
</tr>
<tr>
<td>Male</td>
<td>78</td>
</tr>
<tr>
<td>White</td>
<td>86</td>
</tr>
<tr>
<td>ECOS PS 0/1</td>
<td>54/46</td>
</tr>
<tr>
<td>Baseline hemoglobin ≥ 100 g/L</td>
<td>82</td>
</tr>
<tr>
<td>Baseline site of mets</td>
<td></td>
</tr>
<tr>
<td>Visceral</td>
<td>84</td>
</tr>
<tr>
<td>Liver</td>
<td>28</td>
</tr>
<tr>
<td>LN only</td>
<td>16</td>
</tr>
<tr>
<td>CNS</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristic, %</th>
<th>Nivolumab (N = 270)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of previous regimens for metastatic disease</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>29</td>
</tr>
<tr>
<td>1</td>
<td>42</td>
</tr>
<tr>
<td>2</td>
<td>21</td>
</tr>
<tr>
<td>≥ 3</td>
<td>8</td>
</tr>
<tr>
<td>Previous therapy</td>
<td></td>
</tr>
<tr>
<td>Neoadjuvant/adjuvant platinum-based</td>
<td>34</td>
</tr>
<tr>
<td>Platinum-based*</td>
<td>66</td>
</tr>
<tr>
<td>Cisplatin-based*</td>
<td>39</td>
</tr>
<tr>
<td>Carboplatin-based*</td>
<td>26</td>
</tr>
<tr>
<td>Both cisplatin- and carboplatin-based*</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

*In advanced or metastatic settings.

**Checkmate-275: Efficacy**

<table>
<thead>
<tr>
<th>Parameter, %</th>
<th>Nivolumab (N = 265)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>19.6</td>
</tr>
<tr>
<td>▪ CR</td>
<td>2</td>
</tr>
<tr>
<td>▪ PR</td>
<td>17</td>
</tr>
<tr>
<td>▪ SD</td>
<td>23</td>
</tr>
<tr>
<td>ORR by PD-L1 status</td>
<td></td>
</tr>
<tr>
<td>▪ &lt; 1%</td>
<td>16.1</td>
</tr>
<tr>
<td>▪ ≥ 1%</td>
<td>23.8</td>
</tr>
<tr>
<td>▪ ≥ 5%</td>
<td>28.4</td>
</tr>
<tr>
<td>TTR, mos (range)</td>
<td>1.87 (1.81-1.97)</td>
</tr>
<tr>
<td>DoR, mos (range)</td>
<td>NR (7.43-NR)</td>
</tr>
</tbody>
</table>


![Graph showing median OS (95% CI) with different PD-L1 statuses, All treated pts (n = 265): 8.74 (6.05-NR). PD-L1 < 1% (n = 143): 5.95 (4.30-8.08). PD-L1 ≥ 1% (n = 122): 11.30 (8.74-NR).]
KEYNOTE-045: Study Design

- Randomized phase III trial

Pts with metastatic or locally advanced UC after recurrence or progression following platinum-based chemotherapy; ECOG PS ≤ 2; evaluable tumor tissue for PD-L1 testing (N = 542)

- Primary endpoints: OS; PFS in overall, PD-L1 CPS ≥ 10% populations

- Secondary endpoints: ORR; DoR in overall, PD-L1 CPS ≥ 10% populations; safety

*Select pts allowed to continue treatment beyond initial radiographic progression.
KEYNOTE-045: Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pembro (n = 270)</th>
<th>Chemo (n = 272)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, yrs (range)</td>
<td>67.0 (29-88)</td>
<td>65.0 (26-84)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>200 (74.1)</td>
<td>202 (74.3)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>188 (69.6)</td>
<td>201 (73.9)</td>
</tr>
<tr>
<td>Asian</td>
<td>64 (23.7)</td>
<td>58 (21.3)</td>
</tr>
<tr>
<td>Other/not specified</td>
<td>18 (6.7)</td>
<td>13 (4.8)</td>
</tr>
<tr>
<td>Current or former smoker, n (%)</td>
<td>165 (61.1)</td>
<td>186 (68.4)</td>
</tr>
<tr>
<td>Upper tract disease (renal pelvis/ureter), n (%)</td>
<td>38 (14.3)</td>
<td>36 (14.1)</td>
</tr>
<tr>
<td>PD-L1 CPS ≥ 1%, n (%)</td>
<td>107 (40.2)</td>
<td>108 (42.4)</td>
</tr>
<tr>
<td>PD-L1 CPS ≥ 10%, n (%)</td>
<td>74 (27.4)</td>
<td>90 (33.1)</td>
</tr>
<tr>
<td>Hemoglobin ≥ 10 g/dL</td>
<td>219 (81.1)</td>
<td>223 (82.0)</td>
</tr>
<tr>
<td>ECOG PS*§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>119 (44.1)</td>
<td>106 (39.0)</td>
</tr>
<tr>
<td>1</td>
<td>143 (53.0)</td>
<td>158 (58.1)</td>
</tr>
<tr>
<td>2</td>
<td>2 (0.7)</td>
<td>4 (1.5)</td>
</tr>
<tr>
<td>Visceral disease</td>
<td>240 (88.9)</td>
<td>233 (85.7)</td>
</tr>
<tr>
<td>Liver metastases</td>
<td>91 (33.7)</td>
<td>95 (34.9)</td>
</tr>
<tr>
<td>Time since completion of most recent prior therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 3 mos</td>
<td>166 (61.5)</td>
<td>167 (61.4)</td>
</tr>
<tr>
<td>&lt; 3 mos</td>
<td>103 (38.1)</td>
<td>104 (38.2)</td>
</tr>
</tbody>
</table>


**KEYNOTE-045: OS**

<table>
<thead>
<tr>
<th></th>
<th>Events, n</th>
<th>Median OS, Mos (95% CI)</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>155</td>
<td>10.3 (8.0-11.8)</td>
<td>0.73</td>
<td>.0022</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>179</td>
<td>7.4 (6.1-8.3)</td>
<td>0.73 (0.59-0.91)</td>
<td>.0022</td>
</tr>
</tbody>
</table>

- **Pts at Risk, n**
  - Pembrolizumab: 270 226 194 169 147 131 87 54 27 13 4 0 0 0
  - Chemotherapy: 272 232 171 138 109 89 55 27 14 3 0 0 0

Data cutoff: September 7, 2016

KEYNOTE-045: OS in Pts With PD-L1 CPS ≥ 10%


Data cutoff: September 7, 2016.

<table>
<thead>
<tr>
<th>Events, n</th>
<th>Pembrolizumab</th>
<th>Median OS, Mos (95% CI)</th>
<th>Chemotherapy</th>
<th>Median OS, Mos (95% CI)</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>44</td>
<td>8.0 (5.0-12.3)</td>
<td>0.57 (0.37-0.88)</td>
<td>60</td>
<td>5.2 (4.0-7.4)</td>
<td></td>
<td>.0048</td>
</tr>
</tbody>
</table>

Pembrolizumab

Chemotherapy

Pts at Risk, n

Pembrolizumab: 74 60 51 42 35 31 18 12 7 3 0 0 0
Chemotherapy: 90 76 51 36 28 24 16 8 4 1 0 0 0
KEYNOTE-045: Confirmed ORR

**Total Population**

<table>
<thead>
<tr>
<th>ORR (%</th>
<th>Pembrolizumab (n = 270)</th>
<th>Chemotherapy (n = 272)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>14.1</td>
<td>11.4</td>
</tr>
<tr>
<td>PR</td>
<td>7.0</td>
<td>7.0</td>
</tr>
</tbody>
</table>

**Δ9.6**

**P = .0011**

**ORR assessed per RECIST v1.1 by blinded independent clinical review. No alpha for ORR comparison in PD-L1 CPS ≥ 10% population.**

**Data cutoff: September 7, 2016.**

KEYNOTE-045: Safety

Data cutoff: September 7, 2016.
KEYNOTE-052: First-line Pembrolizumab for Cisplatin-Ineligible Advanced Urothelial Cancer

- Open-label, multicenter phase II study: Current preplanned interim analysis on first 100 pts to evaluate ORR, determine PD-L1–high expression cutoff

Cisplatin-ineligible* pts with advanced UC without prior chemotherapy for metastatic disease; ECOG PS ≤ 2; evaluable tumor tissue for PD-L1 testing (Planned N = 350)

- Primary endpoint: ORR in all pts, ORR in PD-L1–positive pts

- Secondary endpoints: DoR, PFS, OS, ORR in all pts, in PD-L1–positive pts, and in PD-L1–high expressing pts; safety/tolerability; establish PD-L1 high expression cutoff

Pembrolizumab 200 mg Q3W

Treated up to 24 mos or until CR, PD, unacceptable AE, or investigator decision†

ORR assessed per RECIST v1.1 by blinded independent clinical review. No alpha for ORR comparison in PD-L1 CPS ≥ 10% population.

Data cutoff: September 7, 2016.

### KEYNOTE-052: Pembrolizumab Efficacy

<table>
<thead>
<tr>
<th>Outcome (N = 100)</th>
<th>n</th>
<th>% (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR* (CR + PR)</td>
<td>24</td>
<td>24 (16-34)</td>
</tr>
<tr>
<td>- CR</td>
<td>6</td>
<td>6 (2-13)</td>
</tr>
<tr>
<td>- PR</td>
<td>18</td>
<td>18 (11-27)</td>
</tr>
<tr>
<td>SD</td>
<td>15</td>
<td>15 (9-24)</td>
</tr>
<tr>
<td>PD</td>
<td>48</td>
<td>48 (38-58)</td>
</tr>
<tr>
<td>Not evaluable†</td>
<td>3</td>
<td>3 (1-9)</td>
</tr>
<tr>
<td>No assessment‡</td>
<td>10</td>
<td>10 (5-18)</td>
</tr>
</tbody>
</table>

*Confirmed ORR per RECIST v1.1 by central review.
†n = 3 pts achieved SD within 6 wks of treatment start, then discontinued.
‡n = 10 pts withdrew from study due to PD or AE.
Data cutoff: June, 2016.

KEYNOTE-052: Treatment Exposure and Response Duration

- Median follow-up: 8 mos (range: 0.1-13.4)
- Median time to response: 2.0 mos (range: 1.9-4.8)
- Median duration of response: NR (range: 1.4+ to 9.8+)
  - Duration of response ≥ 6 mos: 83%

Duration of Response in Pts with CR or PR as Best Response


Only confirmed responses included. Data cutoff: June 1, 2016.
Case 1: Conclusion

- Our patient tolerated treatment with atezolizumab as part of a clinical trial
- Follow-up CT scans reveal:
Biomarkers for Outcomes with Immune Checkpoint Inhibitors in Advanced UC
Mutation Load and Survival With Atezolizumab in Urothelial Cell Carcinoma

IMvigor210 Cohort 1[1]

IMvigor210 Cohort 2[2]

Responses by Mutation Load[2]

Higher No. Alterations Correlates With Greater Probability of Response to Cisplatin-Based Neoadjuvant Chemotherapy

**MSKCC/DFCI Discovery Cohort**
Higher total number of alterations in responders (pT0/Tis) vs non-responders (≥ pT2) (9.7 vs 4.4 mut/Mb, $P = .0003$)


**FCCC AMVAC Discovery Cohort**
Higher total no. of alterations in responders (pT0) vs other (mean no. alterations: 25.0 vs 18.6, $P = .024$)


**FCCC DDGC Validation Cohort**
Higher total no. of alterations in responders (pT0) vs other (mean no. alterations 22.7 vs 15.3, $P = .018$)


---

**Graphs and Figures**

- **Graph 1:** Distribution of mutations/Mb in responders vs non-responders.
- **Graph 2:** Comparison of residual MIBC and response level (≤ pT1).
- **Graph 3:** Analysis of panel alterations in different categories (Stop, Indel, Splice, Loss, Amplification, Missense) for responders vs non-responders.
Mutation Load Represented by FoundationOne Genes Correlates With Mutation Load in TCGA Whole-Exome Sequencing

- To estimate mutation load, we used a 315-gene FoundationOne panel that covers 3% of the exome\(^1\)

- Whole-exome results correlated with the FoundationOne regions, indicating that the restricted target region was sufficient to rank patients based on mutation load

\(^a\) Spearman \(\rho\) coefficient.
Data cutoff: March 14, 2016.

**IMvigor 210: Response to Atezolizumab by PD-L1 Expression**

<table>
<thead>
<tr>
<th></th>
<th>IC2/3 (n = 100)</th>
<th>IC1/2/3 (n = 207)</th>
<th>All Pts (N = 310)</th>
<th>IC1 (n = 107)</th>
<th>IC0 (n = 103)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR per IRF RECIST v1.1,* % (95% CI)</td>
<td>28 (19-38)</td>
<td>19 (14-25)</td>
<td>16 (12-20)</td>
<td>11 (6-19)</td>
<td>9 (4-16)</td>
</tr>
<tr>
<td>CR rate per IRF RECIST v1.1, † % (95% CI)</td>
<td>14 (8-22)</td>
<td>8 (5-13)</td>
<td>6 (4-9)</td>
<td>3 (1-8)</td>
<td>2 (0-7)</td>
</tr>
<tr>
<td>ORR per immune-modified RECIST, % (95% CI)</td>
<td>29 (20-39)</td>
<td>24 (18-30)</td>
<td>20 (15-25)</td>
<td>19 (12-27)</td>
<td>12 (6-19)</td>
</tr>
</tbody>
</table>

IRF, independent review facility

* n = 17 pts with missing/unevaluable responses not included.
† n = 20 pts with missing/unevaluable responses not included.

- **Median treatment duration: 12 wks (range: 0-104)**
  - 137 pts treated beyond RECIST v1.1 progression
## KEYNOTE-052: Response to Pembrolizumab by PD-L1 Expression

<table>
<thead>
<tr>
<th>Response</th>
<th>PD-L1 CPS &lt; 1%† (n = 33)</th>
<th>PD-L1 CPS ≥ 1% to &lt; 10% (n = 33)</th>
<th>PD-L1 CPS ≥ 10% (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>% (95% CI)</td>
<td>n</td>
</tr>
<tr>
<td>ORR*</td>
<td>6</td>
<td>18 (7-36)</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>3 (0.1-16.0)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>15 (5-32)</td>
<td>5</td>
</tr>
<tr>
<td>SD</td>
<td>3</td>
<td>9 (2-24)</td>
<td>5</td>
</tr>
</tbody>
</table>

*Confirmed ORR per RECIST v1.1 by central review.  
†Excluding those with CPS unknown.  
Data cutoff: June, 2016.

UROTHELIAL CANCER
Histologic Variants

• Cell Types
  • Epithelial: Transitional Cell Carcinoma (TCC)
    – 90-95% of bladder cell malignancies
    – either in pure form or mixed with other elements
  • Squamous Cell Carcinoma - 5% in US
    - risk factors chronic inflammation
      from stones, UTI
    - 75% in Middle East (infx schistosomiasis)
  • AdenoCA/Small Cell CA/LMSarcoma
    – 0.5-2%
• WHO/ISUP Grading
  • Low grade (G1)
  • High grade (G2)

Discovery of molecular subtypes

Intrinsic subtypes of high-grade bladder cancer reflect the hallmarks of breast cancer biology

Jeffrey S. Damrauer1,*, Katherine A. Hoadley2,*, David D. Chion3,*, Cheng Fan1,*, Christopher J. Tiganelli1,*, Sara E. Wobber5,*, Jen Jen Yeh5,*, Matthew I. Milowsky1,*, Gopa Iyer9,*, Joel S. Parker1,*, and William Y. Kim3,*,1

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2Department of Urology, Vanderbilt University Medical Center, Nashville, Tennessee, USA
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8Department of Radiation Oncology, The Ohio State University Wexner Medical Center, Columbus, OH 43210, USA
9Department of Urology, University Hospital, 1020 Willard Street, Suite 701, Philadelphia, PA 19101, USA

*These authors contributed equally to this work.

Abstract

Purpose: Even though urothelial cancer is the fourth most common tumor type among males, progress in treatment has been scarce. A problem in day-to-day clinical practice is that precise assessment of individual tumors is not available. We sought to define whether there are intrinsic molecular subtypes of high-grade bladder cancer. Using gene expression data from a meta-dataset of high-grade, muscle-invasive bladder tumors identified two intrinsic, molecular subsets of high-grade bladder cancer, termed "luminal" and "basal-like," which have characteristics of different stages of urothelial differentiation. The molecular subtypes appear to reflect different stages of urothelial differentiation, reflecting intrinsic and extrinsic factors that contribute to tumor heterogeneity. A gene set predictor, bladder cancer analysis by expression (BASE), which can accurately classify high-grade muscle-invasive bladder tumors into luminal and basal-like tumor subtypes, appears to be an effective tool for clinical decision-making.

Results

We performed an unsupervised clustering analysis on a meta-dataset of high-grade, muscle-invasive bladder cancer samples from 80 patients. The samples were classified into two distinct molecular subtypes: a luminal subtype and a basal-like subtype. The luminal subtype was characterized by the expression of genes associated with differentiation and proliferation, while the basal-like subtype was characterized by the expression of genes associated with invasiveness and metastasis. These results suggest that the molecular subtypes may represent different stages of urothelial differentiation.

Identification of Distinct Basal and Luminal Subtypes of Muscle-Invasive Bladder Cancer with Different Sensitivities to Frontline Chemotherapy

Woojung Choi1, Sima Porten1, Seungchan Kim3,†, Daniel Wilks1,†, Elizabeth R. Pimlott4,†, Jean Hoffman-Consulate1,†, Brian Wills1,†, Tai Soon Chang3,†, Mia Tsao3,†, Ling Lee4,†, Jonathan Marques4,†, Julieta Borell4,†, Cezar Topalian5,†, Shahram Zanger5,†, Steven A.汴6,†, Keith Slugg7,†, Arlene Sieracki-Radtke1,†, Bogdan Czerniak1,†, Cole P.N. Donnay1,†, and David J. McComsey1,†

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Correspondence: dmc@mdanderson.org
http://dx.doi.org/10.1038/ncb2985

OPEN
Subtype calls of all methods in NAC dataset

Presented By Roland Seiler at 2017 Genitourinary Cancers Symposium
Claudin-low tumors in MIBC

**EMT**

**Immune-infiltration/-signaling**

Presented By Roland Seiler at 2017 Genitourinary Cancers Symposium
Classes in Single Sample Classifier (GSC)

Genomic Subtyping Classifier = GSC
Clinical significance: Pathological downstaging

Primary tumor stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>pT3/4</th>
<th>pT2</th>
<th>pT&lt;2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Claudin-low</td>
<td>4</td>
<td>14</td>
<td>24</td>
</tr>
<tr>
<td>Basal</td>
<td>23</td>
<td>31</td>
<td>31</td>
</tr>
<tr>
<td>Luminal-inf</td>
<td>16</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Luminal</td>
<td>27</td>
<td>26</td>
<td>56</td>
</tr>
</tbody>
</table>
Clinical significance: Overall survival

without chemotherapy

- Claudin-low
- Basal
- Luminal-inf
- Luminal

Presented By Roland Seiler at 2017 Genitourinary Cancers Symposium
Clinical significance: Within subtypes

Luminal tumors in NAC dataset

Basal tumors in NAC dataset

- Luminal tumors: p = 0.002
- Basal tumors: p = 0.3
TCGA Subtype II Is Associated With Higher ORR

Gene expression data used to classify IMvigor210 tumor samples recapitulated TCGA subtypes\(^1,2\)

Responses occurred in all subtypes, but ORR was significantly higher in luminal II vs other subtypes \((P = 0.0072)\)

---


Presented By Jonathan Rosenberg at 2016 ASCO Annual Meeting
Immune Checkpoint Inhibitors in UC: Quest for Pt Selection Criteria

- Putative biomarkers: PD-L1?
  - Same issues as seen in melanoma
  - **ORR in PD-L1**—“negative” patients prevents use of PD-L1 expression as a selection criteria

- Heterogeneity may be related to:
  - Antibody and cutoff used
  - Staining performed (tumor cell [TC], IC, type of IC)
  - Tumor heterogeneity
  - Impact of prior therapy/dynamic biomarker
  - Type of target (PD-1/PD-L1)

Immune Checkpoint Inhibitors in UC: Other Potential Biomarkers

- TCR expansion
- Immune signature
- CD8 infiltrate
- Tumor microenvironment
  - Expression of immunosuppressive cytokines
  - Infiltrating Tregs/newly recognized Bregs
- Host factors: microbiota

Management of Adverse Events with Immune Checkpoint Inhibitors in Advanced UC
Immune-Related AEs Seen With Immune Checkpoint Inhibitors

- Hypophysitis
- Uveitis
- Orbital inflammation
- Dry mouth
- Hypothyroidism
- Pneumonitis
- Hepatitis
- Adrenal insufficiency
- Pancreatitis
- Enterocolitis
- Autoimmune diabetes
- Rash and vitiligo
- Arthralgia

Nivolumab Monotherapy Safety: A Pooled Analysis in Advanced Melanoma

- 576 pts with melanoma treated on 4 studies with single-agent nivolumab
  - 10% of pts experienced grade 3/4 treatment-related AEs
  - 24% of pts treated with systemic immunomodulatory drugs (ie, steroids) to manage AEs

- Receipt of immunomodulatory drugs had no effect on overall response rate
  - 29.8% for pts who received IMs vs 31.8% for pts who did not

- Adjusting for number of nivolumab doses, ORR was higher in pts who experienced treatment-related AEs of any grade vs those who did not
  - Can treatment-related AEs predict efficacy?
  - Do responding pts stay on treatment longer and thus are more prone to AEs?

Median Time to Onset and Resolution of Treatment-Related AEs of Any Grade

- n = 474 pts from phase III trials

### Time to Onset

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence (%)</th>
<th>Median Wks (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>33%</td>
<td>5.0 (0.1-57.0)</td>
</tr>
<tr>
<td>GI</td>
<td>14%</td>
<td>7.3 (0.1-37.6)</td>
</tr>
<tr>
<td>Endocrine</td>
<td>8%</td>
<td>10.4 (3.6-46.9)</td>
</tr>
<tr>
<td>Hepatic</td>
<td>4%</td>
<td>7.7 (2.0-38.9)</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>2%</td>
<td>8.9 (3.6-22.1)</td>
</tr>
<tr>
<td>Renal</td>
<td>2%</td>
<td>15.1 (3.9-26.4)</td>
</tr>
</tbody>
</table>

### Time to Resolution

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence (%)</th>
<th>Median Wks (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>47%</td>
<td>18.0 (0.1-68.3+)</td>
</tr>
<tr>
<td>GI</td>
<td>85%</td>
<td>1.2 (0.1-40.0+)</td>
</tr>
<tr>
<td>Endocrine</td>
<td>42%</td>
<td>28.0 (0.9-48.1+)</td>
</tr>
<tr>
<td>Hepatic</td>
<td>68%</td>
<td>3.1 (0.7-17.1)</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>56%</td>
<td>6.0 (1.0-10.1+)</td>
</tr>
<tr>
<td>Renal</td>
<td>88%</td>
<td>4.0 (2.1-20.4+)</td>
</tr>
</tbody>
</table>

n, %: AE incidence.

n, %: pts whose AE resolved.

Kinetics of Onset and Resolution of PD-1/PD-L1 Treatment-Related Skin and GI AEs (≥ 10% of Pts)

Approximate Proportion of Pts (%)

Median Time (wks)

*Any grade.

Kinetics of Onset and Resolution of Less Common PD-1/PD-L1 Treatment-Related AEs (< 10% of Pts)

*Any grade.

Occurrence of New PD-1/PD-L1 Treatment-Related Select AEs of Any Grade Over Time

**Pts**
- Still in study, n: 453, 281, 138, 26, 10, 9
- Still in study receiving treatment, n: 298, 172, 76, 11, 3, 0
- Total with new event, n: 239, 34, 4, 5, 0, 0
- Still in study with new event, %: 53, 12, 3, 19, 0, 0

Patient Case

- A 56-year-old woman with metastatic RCC has been on nivolumab for 3 wks on study when routine TSH returns low
- Heart rate in clinic is 100 with intermittent palpations; she is symptomatic
- Additional testing reveals:

<table>
<thead>
<tr>
<th>Lab</th>
<th>Value</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH, MIU/L</td>
<td>0.002</td>
<td>0.46-4.70</td>
</tr>
<tr>
<td>Free T4, ng/dL</td>
<td>5.1</td>
<td>0.58-1.64</td>
</tr>
<tr>
<td>Free T3, pg/dL</td>
<td>1405</td>
<td>250-390</td>
</tr>
<tr>
<td>Thyroglobulin Ab, IU/mL</td>
<td>48.7</td>
<td>0-4.0</td>
</tr>
</tbody>
</table>
Which is the most appropriate course of action for this patient?

A. Hold nivolumab; hospitalization for IV steroids with plan to taper to PO as outpatient

B. Hold nivolumab; oral methylprednisolone administration as outpatient with repeat lab work and visit in 1 wk

C. Continue nivolumab; initiate beta blocker as outpatient and repeat labs in 1 wk

D. Continue nivolumab; no additional treatment indicated but repeat labs in 3 wks
A Clinician’s Guide to Managing Immune-Related AEs: An Interactive Algorithm Tool

www.clinicaloptions.com/immuneAEtool
A Clinician’s Guide to Managing Immune-Related AEs: An Interactive Algorithm Tool

Organ System Affected by irAE

What is the severity/type of thyroid dysfunction?
- Asymptomatic TSH elevation
- Symptomatic hypothyroidism
- Symptomatic hyperthyroidism

Expert Insight

Patient Summary
- Which organ system is affected?
  - Endocrine
- Which endocrine gland is affected?
  - Thyroid
- What is the severity/type of thyroid dysfunction?
  - Symptomatic hyperthyroidism

Recommendations
- Monitor TFTs every 1 to 3 weeks
- Endocrinology consult
- Administer medical treatment

www.clinicaloptions.com/immuneAEtool
A Clinician’s Guide to Managing Immune-Related AEs: An Interactive Algorithm Tool

Gastrointestinal irAEs

Grade 1
- Diarrhea: 1-3 stools/day over baseline
- Colitis/enteritis: Asymptomatic

Grade 2
- Diarrhea: 4-6 stools per day over baseline
- Colitis/enteritis: Abdominal pain, blood in stool

Grade 3
- Diarrhea: ≥ 7 stools/day over baseline, incontinence; IV fluids ≥ 24 hours, interfering with ADLs
- Colitis/enteritis: Severe abdominal pain, medical intervention indicated, peritoneal signs

Grade 4
- Diarrhea/colitis/enteritis: Life threatening; perforation; obstruction

www.clinicaloptions.com/immuneAEtool
Management Algorithms Used for Diarrhea/Colitis Following Anti–PD-1 Treatment*

**Nivolumab**
- Grade 1
- Continue

**Symptomatic treatment**
- Administer supportive care

**Steroids**
- Monitor for worsening symptoms; educate pt to report immediately

**Follow-up**
- If symptoms worsen: treat as grade 2 or 3/4

*Diarrhea and colitis to varying severity. Grades correspond to NCI CTCAE v4.0.
clinicaloptions.com/immuneAEtool
Management Algorithms Used for Diarrhea/Colitis Following Anti–PD-1 Treatment*

Grade 2

Hold treatment

Administer supportive care

If > 5 days: 0.5-1 mg/kg/day prednisone equivalents followed by taper†

Resume if:
AE remains at grade 0/1 after steroid taper

Discontinue if:
No improvement or symptoms worsen and increase to 1-2 mg/kg/day prednisone equivalents

Nivolumab
Symptomatic treatment
Steroids
Follow-up

Management Algorithms Used for Diarrhea/Colitis Following Anti–PD-1 Treatment*

Grade 3
- Hold tx; consider discontinuing
- Consider lower-GI endoscopy
- 1-2 mg/kg/day prednisone equivalents followed by taper†

Resume if:
- AE remains at grade 0/1 after steroid taper

Discontinue if:
- If symptoms persist > 3-5 days or recur
  Add noncorticosteroid immunosuppressive

Grade 4
- Discontinue

Nivolumab
- Symptomatic treatment
- Steroids
- Follow-up


*Diarrhea and colitis to varying severity. Grades correspond to NCI CTCAE v4.0. †Add antibiotics; for grade 3, consider hospital admission; for grade 4, hospitalization is recommended.

Managing Immune-Related AEs

- Most immune-related AEs are reversible with immunosuppression through steroid treatment
  - Typically start with high-dose IV and then taper over 1-3 mos
  - Exception: adrenal insufficiency and hypothyroid need replacement hydrocortisone and levothyroxine, respectively, not immunosuppressive doses of steroids
- No evidence that intervening with steroids curtails antitumor efficacy of agent
Most, but Not All, Immune-Related AEs Eventually Resolve

<table>
<thead>
<tr>
<th>Patterns of Resolution, %</th>
<th>Checkmate-063 sqNSCLC Nivo 3 mg/kg Q2W</th>
<th>Checkmate-066 Melanoma Nivo 3 mg/kg Q2W</th>
<th>Keynote-001 and -002 Melanoma All Pembro Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>83</td>
<td>46</td>
<td>73</td>
</tr>
<tr>
<td>GI</td>
<td>83</td>
<td>91</td>
<td>94</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>100</td>
<td>50</td>
<td>65</td>
</tr>
<tr>
<td>Endocrine</td>
<td>50</td>
<td>44</td>
<td>12*-79†</td>
</tr>
<tr>
<td>Renal</td>
<td>71</td>
<td>61</td>
<td>100</td>
</tr>
<tr>
<td>Hepatic</td>
<td>67</td>
<td>46</td>
<td>75</td>
</tr>
</tbody>
</table>

Range for *hypothyroidism and †hyperthyroidism.

Safety Summary

- TFTs, CBCs, LFTs, and metabolic panels should be obtained at each treatment and every 6-12 wks for 6 mos post treatment in all pts receiving immune checkpoint inhibitors.

- ACTH and cortisol should also be checked in pts with fatigue and nonspecific symptoms, as well as testosterone in men.

- Frequency of follow-up testing should be adjusted to individual response and AEs that occur.

- Corticosteroids can reverse nearly all toxicities associated with these agents but should be reserved for grade 3/4, or prolonged grade 2, immune-related AEs.

Future Directions for Immune Checkpoint Inhibitors in Advanced UC
Durvalumab (Anti–PD-L1 Ab): Promising Activity in Advanced UC

- Phase I/II dose escalation and expansion study of durvalumab in advanced or metastatic UBC

<table>
<thead>
<tr>
<th>PD-L1 Expression by Location</th>
<th>PD-L1 Status</th>
<th>ORR, n/N (%)</th>
<th>DCR12*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All evaluable pts</td>
<td>Any</td>
<td>13/42 (31)</td>
<td>20/42 (48)</td>
</tr>
<tr>
<td>TC</td>
<td>+</td>
<td>7/15 (47)</td>
<td>8/15 (53)</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>6/27 (22)</td>
<td>12/27 (44)</td>
</tr>
<tr>
<td>IC</td>
<td>+</td>
<td>10/18 (56)</td>
<td>12/18 (67)</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>3/24 (13)</td>
<td>8/24 (33)</td>
</tr>
<tr>
<td>TC or IC†</td>
<td>+</td>
<td>13/28 (46)</td>
<td>16/28 (57)</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>0/14 (0)</td>
<td>4/14 (29)</td>
</tr>
</tbody>
</table>

*Confirmed CR, PR, or SD for ≥ 12 wks per RECIST v1.1.
†≥ 25% TCs or ICs.

Durvalumab granted breakthrough therapy designation based on these data.

Additional Immunotherapy Approaches for Urothelial Cancer

- Nonmuscle-invasive bladder cancer
  - IV or intravesical anti–PD-1 therapy alone or with BCG
- NMIBC or MIBC or mets
  - Vaccines: NY-ESO-1, MAGE-family, HER2/ERBB2
  - PANVAC: poxviral vector with transgenes for CEA and MUC-1 (expressed in UC), as well as 3 T-cell costimulatory molecules (ie, Tricom)
  - DN24-02: activated autologous APCs; similar to sipuleucel-T

- Combination modalities
  - Immunotherapy plus immunotherapy
  - Immunotherapy plus cytotoxic therapy
  - Immunotherapy plus surgery/XRT

- JAVELIN Bladder 100: Maintenance Avelumab in Metastatic Urothelial Cancer

- DANUBE: First-line Durvalumab ± Tremelimumab vs SoC in Advanced UBC
Efficacy and safety of nivolumab plus ipilimumab in previously treated metastatic urothelial carcinoma

First results from the phase I/II CheckMate 032 study

Padmanee Sharma, Margaret K. Callahan, Emiliano Calvo, Joseph Kim, Filippo de Braud, Patrick A. Ott, Petri Bono, Rathi N. Pillai, Michael Morse, Dung T. Le, Matthew Taylor, Pavlina Spiliopoulou, Johanna Bendell, Dirk Jaeger, Emily Chan, Scott Antonia, Paolo A. Ascierto, Delphine Hennicken, Marina Tschaika, Alex Azrilevich, Jonathan Rosenberg

1 MD Anderson Cancer Center, University of Texas, Houston, TX, USA; 2 Memorial Sloan Kettering Cancer Center, New York, NY, USA; 3 START Madrid, Centro Integral Oncológico Clara Campal, Madrid, Spain; 4 Yale Cancer Center, New Haven, CT, USA; 5 Istituto Nazionale dei Tumori-Università degli Studi di Milano, Milan, Italy; 6 Dana-Farber Cancer Institute, Boston, MA, USA; 7 Comprehensive Cancer Center, Helsinki University Hospital and University of Helsinki, Helsinki, Finland; 8 Emory Winship Cancer Institute, Atlanta, GA, USA; 9 Duke University Medical Center, Durham, NC, USA; 10 Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA; 11 Oregon Health and Science University, Portland, OR, USA; 12 Beatson West of Scotland Cancer Centre, Glasgow, UK; 13 Tennessee Oncology, Nashville, TN, USA; 14 Heidelberg University Hospital, Heidelberg, Germany; 15 Vanderbilt-Ingram Cancer Center, Nashville, TN, USA; 16 Moffitt Cancer Center, Tampa, FL, USA; 17 Istituto Tumori Napoli Fondazione G. Pascale, Naples, Italy; 18 Bristol-Myers Squibb, Princeton, NJ, USA

Presented By Matthew Milowsky at 2017 Genitourinary Cancers Symposium
CheckMate 032: Study design

Open-label, multicenter, phase I/II study (NCT01928394)

Pretreated patients with locally advanced or metastatic urothelial carcinoma

- Nivolumab 3 mg/kg IV Q2W (N=78)\(^1\)

- Nivolumab 1 mg/kg + ipilimumab 3 mg/kg (NIVO 1 + IPI 3) IV Q3W for 4 cycles (N=26)

- Nivolumab 3 mg/kg + ipilimumab 1 mg/kg (NIVO 3 + IPI 1) IV Q3W for 4 cycles (N=104)

- Treatment beyond progression was permitted if treatment was tolerated and prespecified clinical benefit was noted

- Tumor measurements: CT or MRI every 6 weeks (±1 week) from first dose for the first 24 weeks, then every 12 weeks (±1 week)


Presented By Matthew Milowsky at 2017 Genitourinary Cancers Symposium
### Treatment-related and select treatment-related AEs in ≥5% of patients

<table>
<thead>
<tr>
<th>Event, %</th>
<th>NIVO 1 + IPI 3 (N=26)</th>
<th>NIVO 3 + IPI 1 (N=104)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade</td>
<td>Grade 3–4</td>
</tr>
<tr>
<td>All treatment-related AEs</td>
<td>76.9</td>
<td>30.8</td>
</tr>
<tr>
<td>Treatment-related AEs leading to discontinuation</td>
<td>7.7</td>
<td>7.7</td>
</tr>
<tr>
<td>Select (immune-mediated) treatment-related AEs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>42.3</td>
<td>0</td>
</tr>
<tr>
<td>Rash, maculopapular</td>
<td>26.9</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>26.9</td>
<td>7.7</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>15.4</td>
<td>0</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>7.7</td>
<td>3.8</td>
</tr>
<tr>
<td>Colitis</td>
<td>3.8</td>
<td>0</td>
</tr>
<tr>
<td>Elevated ALT</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Elevated AST</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

One treatment-related death reported in the NIVO 3 + IPI 1 group (pneumonitis)
## Antitumor activity

<table>
<thead>
<tr>
<th>Outcome, %</th>
<th>NIVO 1 + IPI 3 (N=26)</th>
<th>NIVO 3 + IPI 1 (N=104)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed ORR, %</td>
<td>38.5</td>
<td>26.0</td>
</tr>
<tr>
<td>95% CI</td>
<td>20.2–59.4</td>
<td>17.9–35.5</td>
</tr>
<tr>
<td>Best overall response, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>3.8</td>
<td>2.9</td>
</tr>
<tr>
<td>Partial response</td>
<td>34.6</td>
<td>23.1</td>
</tr>
<tr>
<td>Stable disease</td>
<td>19.2</td>
<td>25.0</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>26.9</td>
<td>41.3</td>
</tr>
</tbody>
</table>
Overall survival

Median OS, months (95% CI)

- NIVO 1 + IPI 3: 10.2 (4.5–NR)
- NIVO 3 + IPI 1: 7.3 (5.6–11.4)

No. at risk

NIVO 1 + IPI 3  26  21  17  7  3  3  3  2  1  0
NIVO 3 + IPI 1  104  84  59  45  38  27  8  0  0  0
# Summary: Current Status of Immune Checkpoint Inhibitors for Pts With LA or mUC

<table>
<thead>
<tr>
<th>Agent</th>
<th>FDA Status</th>
<th>Patient population</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atezolizumab</td>
<td>Approved</td>
<td>Pts with PD during or following platinum chemotherapy or within 12 mos of (neo)adjuvant platinum chemotherapy</td>
<td>Breakthrough status for first-line therapy for cisplatin-ineligible pts</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>Approved</td>
<td>Pts with PD during or following platinum chemotherapy or within 12 mos of (neo)adjuvant platinum chemotherapy</td>
<td></td>
</tr>
<tr>
<td>Durvalumab</td>
<td>Breakthrough therapy</td>
<td>Pts with PD after progression on or after 1 previous platinum chemotherapy</td>
<td>Under priority review, with PDUFA set for the second quarter of 2017</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>Breakthrough therapy</td>
<td>First-line: pts who are ineligible for cisplatin-containing therapy or Second-line: Pts with PD during or following platinum chemotherapy</td>
<td>Under priority review, with PDUFA set for June 2017</td>
</tr>
<tr>
<td>Avelumab</td>
<td>---</td>
<td></td>
<td>Currently in clinical trials</td>
</tr>
</tbody>
</table>
Thank you and Questions?