Immunotherapy of Prostate Cancer, Bladder Cancer and Renal Cell Cancer

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Johns Hopkins Sidney Kimmel Cancer Center
Introduction to Immunotherapy

DS. Chen and I. Mellman. 
Oncology Meets Immunology: 
The Cancer-Immunity Cycle. 
Immunity 39, July 25, 2013
Introduction to Immunotherapy

Tumor Cell

Dendritic Cell

Tissue Macrophage

Costimulatory checkpoints in tumor microenvironment
Introduction to Immunotherapy
Introduction to Immunotherapy
Immune Checkpoint Inhibitors
Prostate Cancer
Immune Checkpoint Inhibitors
Prostate Cancer: Ipilimumab (post-docetaxel)

**CA184-043: Study design**

- **Post-docetaxel CRPC (N = 799)**
  - Patients stratified by investigator site, alkaline phosphatase, haemoglobin, and ECOG PS

- **Screening**
  - *1:1*

- **Single-dose, bone-directed RT (8 GY)**
  - **N = 399**
    - Ipilimumab (10 mg/kg)
      - Wks 1, 4, 7, 10
      - Every 12 wks

- **N = 400**
  - Placebo
    - Wks 1, 4, 7, 10
  - Placebo
    - Every 12 wks

- **Treatment until disease progression or intolerable toxicity**

- **Primary endpoint:** OS
- **Secondary endpoints:** Progression-free survival, safety
- **Exploratory endpoint:** PSA response rate

Immune Checkpoint Inhibitors
Prostate Cancer: Ipilimumab (post-docetaxel)


No significant clinical difference

Ipilimumab (pre-docetaxel): no significant difference
Immune Checkpoint Inhibitors
Prostate Cancer: PDL-1 expression

Enzalutamide resistant PC cell lines

High expression PDL-1 in human primary PC

Heidrun Gebensleben et al, CCR nov 2015
Massari et al. Target Oncol nov 2015
Immune Checkpoint Inhibitors
Prostate Cancer

Real Men and Women
Still believe in Immunotherapy
of Prostate Cancer
Immune Checkpoint Inhibitors
Bladder Cancer

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Immune Checkpoint Inhibitors
Bladder Cancer

PDL-1 = B7 homolog 1

Boorijan SA et al, CCR 2008
Immune Checkpoint Inhibitors
Bladder Cancer: PDL-1 expression

Immune Checkpoint Inhibitors
Bladder Cancer

<table>
<thead>
<tr>
<th>PD-L1 prevalence in UBC tumours by IHC</th>
<th>PD-L1-positive tumour-infiltrating immune cells (no. of specimens (%))</th>
<th>PD-L1-positive tumour cells (no. of specimens (%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 205</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IHC 3</td>
<td>18 (9)</td>
<td>14 (7)</td>
</tr>
<tr>
<td>IHC 2</td>
<td>37 (18)</td>
<td>8 (4)</td>
</tr>
<tr>
<td>IHC 1</td>
<td>89 (43)</td>
<td>37 (18)</td>
</tr>
<tr>
<td>IHC 0</td>
<td>61 (30)</td>
<td>146 (71)</td>
</tr>
</tbody>
</table>
Immune Checkpoint Inhibitors
Bladder Cancer: Atezolizumab

By leaving the PD-L2/PD-1 interaction intact, atezolizumab has the potential to preserve peripheral immune homeostasis.
## Immune Checkpoint Inhibitors
Bladder Cancer: PDL-1 expression and response

<table>
<thead>
<tr>
<th>Tumour-infiltrating immune cells and objective response rates</th>
<th>Objective response rate</th>
<th>Stable disease</th>
<th>Progressive disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>IHC 2/3 (n = 30)</td>
<td>13 (43.3)</td>
<td>8 (26.7)</td>
<td>8 (26.7)</td>
</tr>
<tr>
<td>(95% CI: 25.5–62.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IHC 3 (n = 10)</td>
<td>5 (50.0)</td>
<td>2 (20.0)</td>
<td>3 (30.0)</td>
</tr>
<tr>
<td>(95% CI: 22.2–77.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IHC 2 (n = 20)</td>
<td>8 (40.0)</td>
<td>6 (30.0)</td>
<td>5 (25.0)</td>
</tr>
<tr>
<td>(95% CI: 20.9–63.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IHC 0/1 (n = 35)</td>
<td>4 (11.4)</td>
<td>13 (37.1)</td>
<td>13 (37.1)</td>
</tr>
<tr>
<td>(95% CI: 4.0–26.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IHC 1 (n = 23)</td>
<td>3 (13.0)</td>
<td>8 (34.8)</td>
<td>8 (34.8)</td>
</tr>
<tr>
<td>(95% CI: 3.7–31.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IHC 0 (n = 12)</td>
<td>1 (8.3)</td>
<td>5 (41.7)</td>
<td>5 (41.7)</td>
</tr>
<tr>
<td>(95% CI: 0.4–34.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IMvigor 210: PD-L1 IHC
PD-L1 Immune Cell Expression and Prevalence

IHC Status of Treated Patients in IMvigor 210 Study (N = 311)

- IMvigor 210 enrolled an all-comer population
- VENTANA PD-L1 (SP142) CDx Assay was used to prospectively measure tumor-infiltrating immune cell (IC) PD-L1 expression based on 3 IHC scoring levels

Images at 10x magnification.

Rosenberg JE, et al.: IMvigor 210: Phase II Atezolizumab in mUC
IMvigor 210: Efficacy
Changes in Target Lesions by PD-L1 Subgroup

51/85 (60%) PD-L1 status
IC2/3 ORR\textsuperscript{b} 27%

38/88 (43%) IC1 10%

27/85 (32%) IC0 9%

111/258 (43%) patients with tumor assessments had SLD reduction

SLD, sum of longest diameters. \textsuperscript{a} > 100% increase. \textsuperscript{b} Per confirmed RECIST v1.1 (independent review).

Data cutoff May 5, 2015. Follow up \geq 24 weeks. Patients without post-baseline tumor assessments not included.
Several patients with CR had < 100% reduction due to lymph node target lesions. All lymph nodes returned to normal size per RECIST v1.1.
IMvigor 210: Efficacy
Preliminary Analyses of Overall Survival

Survival

<table>
<thead>
<tr>
<th></th>
<th>IC2/3 n = 100</th>
<th>IC0/1 n = 211</th>
<th>All N = 311</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, mo (95% CI)</td>
<td>NR (7.6, NE)</td>
<td>6.7 (5.7, 8.0)</td>
<td>7.9 (6.7, NE)</td>
</tr>
</tbody>
</table>

Median follow up: 7 mo (range, 0-11 mo)

NR, not reached; NE, not estimable. Data cutoff May 5, 2015. Follow up ≥ 24 weeks.

Rosenberg JE, et al.: IMvigor 210: Phase II Atezolizumab in mUC
IMvigor 210: Safety Summary

<table>
<thead>
<tr>
<th>AE (N = 311)</th>
<th>All Cause</th>
<th>Treatment Related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Grade</td>
<td>96%</td>
<td>66%</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>45%</td>
<td>11%</td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>50%</td>
<td>15%</td>
</tr>
<tr>
<td>Grade 5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>AEs leading to withdrawal</td>
<td>3%</td>
<td>N/A</td>
</tr>
<tr>
<td>AEs leading to dose modification/interruption</td>
<td>27%</td>
<td>N/A</td>
</tr>
</tbody>
</table>

- Median treatment duration 12 weeks (range, 0-46 wk) with median of 5 doses (range, 1-16 doses)
- Atezolizumab was well tolerated with no treatment-related deaths
- AE profile was consistent across IC2/3, IC1/2/3 and all-comer populations

<sup>a</sup>2 all-cause Grade 5 AEs were seen: pulmonary sepsis and subileus (intestinal occlusion).

Data cutoff May 5, 2015. Follow up ≥ 24 weeks.

Rosenberg JE, et al.: IMvigor 210: Phase II Atezolizumab in mUC
Immune Checkpoint Inhibitors
Bladder Cancer

Pembrolizumab (MK-3475) for Advanced Urothelial Cancer: Updated Results and Biomarker Analysis from KEYNOTE-012

Elizabeth R. Plimack,¹ Joaquim Bellmunt,² Shilpa Gupta,³ Raanan Berger,⁴ Bruce Montgomery,⁵ Karl Heath,⁶ Jonathan Juco,⁶ Kenneth Emancipator,⁶ Kumudu Pathiraja,⁶ Jared Lunceford,⁶ Rodolfo Perini,⁶ Peter H. O’Donnell⁷

¹Fox Chase Cancer Center, Philadelphia, PA, USA,
²Dana-Farber Cancer Institute, Boston, MA, USA,
³H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA,
⁴Sheba Medical Center, Tel Hashomer, Israel,
⁵University of Washington, Seattle, WA, USA,
⁶Merck & Co., Inc., Kenilworth, NJ, USA,
⁷University of Chicago, Chicago, IL, USA
Immune Checkpoint Inhibitors
Bladder Cancer: Pembroluzimab

Overall Response Rate = 28% (8/33)

64% experienced a decrease in target lesions

Immune Checkpoint Inhibitors
Bladder Cancer: Pembroluzimab

Duration of Response

- Median follow-up duration: 15 (0.6-20) months
- Median time to response: 9 (7.7–55.9) weeks
- Response duration: 8.1 to 64.1+ weeks
- 3 patients remain on therapy

RECIST v1.1, Central Review
Analysis cutoff date: March 23, 2015

Time, weeks

Immune Checkpoint Inhibitors
Bladder Cancer: summary

20 years no improvement in overall survival

Atezolozimab (anti-PDL-1):
• 15% grade 3-4 toxicity
• 37% response rate
• OS: 10-14 months

Pembroluzimab (anti-PD-1):
• 15% grade 3-4 toxicity
• 28% response rate
• OS: 13 months

Docetaxel:
• 15-20% response rate
• OS: 7 months
Immune Checkpoint Inhibitors
Renal Cell Cancer
Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma

Immune Checkpoint Inhibitors
Renal Cell Cancer: Phase III data nivolumab

B Kaplan–Meier Curve for Progression-free Survival

<table>
<thead>
<tr>
<th>Drug</th>
<th>No. of Patients</th>
<th>Median Progression-free Survival (95% CI)</th>
<th>No. of Progression Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>410</td>
<td>4.6 (3.7–5.4)</td>
<td>318</td>
</tr>
<tr>
<td>Everolimus</td>
<td>411</td>
<td>4.4 (3.7–5.5)</td>
<td>322</td>
</tr>
</tbody>
</table>

Hazard ratio, 0.88 (95% CI, 0.75–1.03)
P=0.11

No. at Risk

<table>
<thead>
<tr>
<th>Drug</th>
<th>No. at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>410 230 145 116 81 66 48 29 11 4 0 0 0</td>
</tr>
<tr>
<td>Everolimus</td>
<td>411 227 129 97 61 47 25 16 3 0 0 0 0</td>
</tr>
</tbody>
</table>

Motzer et al *NEJM* 2015
Immune Checkpoint Inhibitors
Renal Cell Cancer: Phase III data nivolumab

Motzer et al *NEJM* 2015
### Immune Checkpoint Inhibitors
Renal Cell Cancer: Phase III data nivolumab

#### A. Subgroup Analyses of Overall Survival

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Nivolumab No. of Events/Total No.</th>
<th>Everolimus No. of Events/Total No.</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 prognostic score</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>Previous antiangiogenic 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>United States or 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</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 yr</td>
<td>111/257</td>
<td>118/240</td>
<td>0.78 (0.60–1.01)</td>
</tr>
<tr>
<td>≥65 to &lt;75 yr</td>
<td>53/119</td>
<td>77/131</td>
<td>0.64 (0.45–0.91)</td>
</tr>
<tr>
<td>≥75 yr</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>
# Immune Checkpoint Inhibitors
Renal Cell Cancer: Phase III data nivolumab

<table>
<thead>
<tr>
<th>Event</th>
<th>Nivolumab Group (N=406)</th>
<th>Everolimus Group (N=397)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3 or 4</td>
</tr>
<tr>
<td>All events</td>
<td>319 (79)</td>
<td>76 (19)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>134 (33)</td>
<td>10 (2)</td>
</tr>
<tr>
<td>Nausea</td>
<td>57 (14)</td>
<td>1 (&lt;1)</td>
</tr>
</tbody>
</table>

*Table 2. Treatment-Related Adverse Events Reported in 10% or More of Treated Patients in Either Group.*
Overall survival by PD-L1 expression

**PD-L1 ≥1% (n = 24%)**

<table>
<thead>
<tr>
<th></th>
<th>Median OS, months (95% CI)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>21.8 (16.5–28.1)</td>
<td>0.79 (0.53–1.17)</td>
</tr>
<tr>
<td>Everolimus</td>
<td>18.8 (11.9–19.9)</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>Median OS, months (95% CI)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>27.4 (21.4–NE)</td>
<td>0.77 (0.60–0.97)</td>
</tr>
<tr>
<td>Everolimus</td>
<td>21.2 (17.7–26.2)</td>
<td></td>
</tr>
</tbody>
</table>
Immune Checkpoint Inhibitors
Renal Cell Cancer: Nivolumab + Ipilimumab

Investigator’s assessment for response (RECIST v1.1)

Screening and every 6 weeks from randomization for first four assessments

Every 12 weeks until disease progression

Previously treated or treatment-naïve patients with mRCCa

Randomization

Arm NIVO3 + IPI1
Nivolumab 3 mg/kg IV + ipilimumab 1 mg/kg IV Q3W × 4

Arm NIVO1 + IPI3
Nivolumab 1 mg/kg IV + ipilimumab 3 mg/kg IV Q3W × 4

Arm NIVO3 + IPI3
Nivolumab 3 mg/kg IV + ipilimumab 3 mg/kg IV Q3W × 4

Continuous nivolumab 3 mg/kg IV Q2W

Primary Endpoint:
Safety
(AEs, serious AEs, laboratory tests)

Secondary Endpoint:
Efficacy
(ORR, DOR, OS, PFS)

For expansion cohorts NIVO3 + IPI1 and NIVO1 + IPI3 and for NIVO3 + IPI3, one prior adjuvant or neoadjuvant therapy for localized or locally advanced RCC is allowed provided recurrence occurred ≥6 months after the last dose of the adjuvant or neoadjuvant therapy. Interferon alpha or interleukin-2 (IL-2) as prior therapy is allowed.

AE = adverse event; DOR = duration of response; IPI1 = ipilimumab 1 mg/kg; IPI3 = ipilimumab 3 mg/kg; IV = intravenous; NIVO1 = nivolumab 1 mg/kg; NIVO3 = nivolumab 3 mg/kg; ORR = objective response rate; PFS = progression-free survival; Q2W = every 2 weeks; Q3W = every 3 weeks; RECIST = Response Evaluation Criteria in Solid Tumors

Hammers et al ASCO 2014
Motzer et al ASCO 2015
Immune Checkpoint Inhibitors
Renal Cell Cancer: Nivolumab + Ipilimumab

<table>
<thead>
<tr>
<th></th>
<th>NIVO3 + IPI1</th>
<th>NIVO1 + IPI3</th>
<th>NIVO3 + IPI3</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 47</td>
<td>N = 47</td>
<td>N = 6</td>
<td></td>
</tr>
<tr>
<td>Confirmed ORR&lt;sup&gt;a&lt;/sup&gt;, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>18 (38.3)</td>
<td>19 (40.4)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>24.5–53.6</td>
<td>26.4–55.7</td>
<td></td>
</tr>
<tr>
<td>Best overall response&lt;sup&gt;b&lt;/sup&gt;, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>4 (8.5)</td>
<td>1 (2.1)</td>
<td>0</td>
</tr>
<tr>
<td>Partial response</td>
<td>14 (29.8)</td>
<td>18 (38.3)</td>
<td>0</td>
</tr>
<tr>
<td>Stable disease</td>
<td>17 (36.2)</td>
<td>17 (36.2)</td>
<td>5 (83.3)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>10 (21.3)</td>
<td>7 (14.9)</td>
<td>1 (16.7)</td>
</tr>
</tbody>
</table>
### Immune Checkpoint Inhibitors
Renal Cell Cancer: Nivolumab + Ipilimumab
Adverse Events

<table>
<thead>
<tr>
<th>Preferred term, n (%)</th>
<th>NIVO3 + IPI1</th>
<th>NIVO1 + IPI3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 47</td>
<td>N = 47</td>
</tr>
<tr>
<td>Total patients with an event</td>
<td>39 (83.0) 16 (34.0)</td>
<td>44 (93.6) 30 (63.8)</td>
</tr>
</tbody>
</table>
Immune Checkpoint Inhibitors
Renal Cell Cancer

Medical benefit

1 2 3

Control Immunotherapy Targeted Therapy Immuno doublets & combos with targeted therapies
Everolimus or axitinib?

First line: Sunitinib, pazopanib
Second line: Nivolumab, cabozantinib
Third line: Nivolumab, cabozantinib
Fourth line: 4th line therapy should focus on drugs not previously given, especially Nivolumab or Cabozantinib

Recommend with OS advantage
Recommended without OS
Recommended if other options
Not available.
Immune Checkpoint Inhibitors