2014 Best of ASCO: Novel Immunotherapy for Kidney (and Bladder) Cancer

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Memorial Sloan-Kettering Cancer Center
Treatment options for patients with mRCC have been revolutionised in a short period of time...

Renal Cell Carcinoma

Clear Cell Carcinoma (75%)
- LOH - 3p25
- VHL mutation (60-70%)
- Hypermethylation (5-20%)

Type 1 c-met mutation
Type 2 FH mutation

Proximal Nephron
- Papillary Carcinoma (15%)

Distal Nephron
- Chromophobe (5%)

Oncocytoma (5%)

Collecting Duct, Undifferentiated (rare)
Phase III Trial Sunitinib vs IFN-α: Progression-free Survival


HR = 0.538
95% CI (0.439, 0.658)

P < .00001

Sunitinib
Median: 11.0 months
(95% CI: 10.7–13.4)

IFN-α
Median: 5.1 months
(95% CI: 3.9–5.6)

No. at Risk
Sunitinib: 375 240 156 54 10 1
IFN-α: 375 124 46 15 4 0

PFS probability
# Treatments for Clear-cell mRCC

<table>
<thead>
<tr>
<th>Setting</th>
<th>Patients</th>
<th>Level 1*</th>
<th>≥ Level 2*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-line</strong></td>
<td>Good- or intermediate-risk</td>
<td><strong>Sunitinib</strong>&lt;br&gt;Bevacizumab + IFN-α&lt;br&gt;Pazopanib</td>
<td>High-dose IL-2</td>
</tr>
<tr>
<td></td>
<td>Poor-risk</td>
<td><strong>Temsirolimus</strong>&lt;br&gt;<strong>Sunitinib</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Second-line</strong></td>
<td>Prior VEGF TKI</td>
<td><strong>Everolimus</strong>&lt;br&gt;Axitinib</td>
<td><strong>Sorafenib</strong></td>
</tr>
</tbody>
</table>

Challenges in Clinical Outcome With Targeted Drugs

- Few complete responses
- Plateau in efficacy
- Primary treatment refractory
- Acquired resistance
- Survival benefit elusive in trials
- Chronic toxicities
Challenges in Clinical Outcome With Targeted Drugs

- Few complete responses
- Plateau in efficacy
- Primary treatment refractory
- Acquired resistance
- Survival benefit elusive in trials
- Chronic toxicities

NEW DRUGS ARE NEEDED WITH A NOVEL MECHANISM OF ACTION
Binding of PD-1 to its ligands PD-L1 and PD-L2 leads to downregulation of the antitumor immune response

Nivolumab is a fully human IgG4 PD-1 immune checkpoint inhibitor

Nivolumab selectively blocks the PD-1 and PD-L1/PD-L2 interaction, restoring antitumor T-cell function

IFNy, interferon gamma; MHC, major histocompatibility complex; PD-1, programmed death-1; PD-L1, programmed death-ligand

ASCO 2014 Abstracts

• Abstract 5009: Nivolumab for metastatic renal cell carcinoma: results of a randomized, dose-ranging phase II trial
• Abstract 5012: Immunomodulatory activity of nivolumab in previously treated and untreated metastatic renal cell carcinoma: biomarker-based results from a randomized clinical trial
• Abstract 5010: Nivolumab in combination with sunitinib or pazopanib in patients with metastatic renal cell carcinoma
• Abstract 4504: Phase I study of nivolumab in combination with ipilimumab in metastatic renal cell carcinoma
Nivolumab for metastatic renal cell carcinoma (mRCC): results of a randomized, dose-ranging phase II trial

Phase II study design

Key Criteria
- mRCC with clear-cell component
- ≥1 prior antiangiogenic agent
- 1–3 prior therapies
- Disease progression after last therapy and within 6 mos of enrollment
- KPS ≥70%
- Adequate organ function

Arm 1
0.3 mg/kg nivolumab IV Q3 weeks

Arm 2
2 mg/kg nivolumab IV Q3 weeks

Arm 3
10 mg/kg nivolumab IV Q3 weeks

Treat until progression or intolerable toxicity

Primary Objective: To assess whether a dose–response relationship exists in the 0.3, 2, and 10 mg/kg arms as measured by PFS (RECIST v1.1)

Secondary Objectives: Estimation of PFS, ORR, OS, and adverse event rate

Exploratory Objectives: Pharmacokinetics, PD-L1 expression (prototype assay)

ClinTrials.gov NCT01354431

*Treatment arms blinded. Stratified by MSKCC prognostic score (0 vs 1 vs 2/3) and number of prior lines of therapy in the metastatic setting (1 vs >1).*
### Prior therapy in metastatic setting

<table>
<thead>
<tr>
<th>Prior nephrectomy, %</th>
<th>0.3 (n = 60)</th>
<th>2.0 (n = 54)</th>
<th>10 (n = 54)</th>
<th>Total (N = 168)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>90</td>
<td>91</td>
<td>94</td>
<td>92</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prior systemic regimens, %</th>
<th>0.3 (n = 60)</th>
<th>2.0 (n = 54)</th>
<th>10 (n = 54)</th>
<th>Total (N = 168)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>27</td>
<td>30</td>
<td>33</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>33</td>
<td>35</td>
<td>43</td>
<td>37</td>
</tr>
<tr>
<td>3</td>
<td>40&lt;sup&gt;a&lt;/sup&gt;</td>
<td>35</td>
<td>24</td>
<td>33</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Common prior systemic therapies, %&lt;sup&gt;b&lt;/sup&gt;</th>
<th>0.3 (n = 60)</th>
<th>2.0 (n = 54)</th>
<th>10 (n = 54)</th>
<th>Total (N = 168)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunitinib</td>
<td>77</td>
<td>78</td>
<td>69</td>
<td>74</td>
</tr>
<tr>
<td>Everolimus</td>
<td>35</td>
<td>33</td>
<td>33</td>
<td>34</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>25</td>
<td>33</td>
<td>24</td>
<td>27</td>
</tr>
<tr>
<td>Interleukin-2</td>
<td>25</td>
<td>20</td>
<td>22</td>
<td>23</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>22</td>
<td>15</td>
<td>19</td>
<td>19</td>
</tr>
</tbody>
</table>

<sup>a</sup>1 patient (2%) in the 0.3 mg/kg group received >3 prior systemic therapies in the metastatic setting. <sup>b</sup>&gt;20% of patients in any group.
Progression-free survival

<table>
<thead>
<tr>
<th>Number of patients at risk</th>
<th>Median PFS, months (80% CI)</th>
<th>Stratified trend test $P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3 mg/kg</td>
<td>2.7 (1.9, 3.0)</td>
<td>0.9</td>
</tr>
<tr>
<td>2 mg/kg</td>
<td>4.0 (2.8, 4.2)</td>
<td></td>
</tr>
<tr>
<td>10 mg/kg</td>
<td>4.2 (2.8, 5.5)</td>
<td></td>
</tr>
</tbody>
</table>

Symbols represent censored observations.

Number of patients at risk

<table>
<thead>
<tr>
<th>0.3 mg/kg</th>
<th>2 mg/kg</th>
<th>10 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>54</td>
<td>54</td>
</tr>
<tr>
<td>24</td>
<td>27</td>
<td>30</td>
</tr>
<tr>
<td>17</td>
<td>15</td>
<td>18</td>
</tr>
<tr>
<td>13</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>12</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>11</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Time (months)

0 3 6 9 12 15 18 21 24
# Objective responses

<table>
<thead>
<tr>
<th>Nivolumab, mg/kg</th>
<th>0.3 (n = 60)</th>
<th>2.0 (n = 54)</th>
<th>10 (n = 54)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR, n (%)&lt;sup&gt;a&lt;/sup&gt;</strong></td>
<td>12 (20)</td>
<td>12 (22)</td>
<td>11 (20)</td>
</tr>
<tr>
<td>(80% CI)</td>
<td>(13.4, 28.2)</td>
<td>(15.0, 31.1)</td>
<td>(13.4, 29.1)</td>
</tr>
<tr>
<td><strong>Duration of response, median (80% CI), months&lt;sup&gt;b&lt;/sup&gt;</strong></td>
<td>NR (NR, NR)</td>
<td>NR (4.2, NR)</td>
<td>22.3 (4.8, NR)</td>
</tr>
<tr>
<td><strong>Best overall response, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Partial response</td>
<td>18</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Stable disease</td>
<td>37</td>
<td>43</td>
<td>44</td>
</tr>
<tr>
<td>Progression</td>
<td>40</td>
<td>33</td>
<td>32</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>3</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

<sup>a</sup>ORR defined by RECIST v1.1; data cutoff May 15, 2013. <sup>b</sup>Derived from the Kaplan–Meier estimate; data cutoff March 5, 2014. NR, not reached.
Duration of response

- 0.3 mg/kg (n=12)
- 2 mg/kg (n=12)
- 10 mg/kg (n=11)

Based on data cutoff of March 5, 2014.
### Treatment-related adverse events (≥10% of patients in any arm)

<table>
<thead>
<tr>
<th>Patients with event, %</th>
<th>Nivolumab, mg/kg</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade</td>
<td>Grade 3-4</td>
<td>Any grade</td>
<td>Grade 3-4</td>
<td>Any grade</td>
<td>Grade 3-4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.3 (n=59)</td>
<td>2.0 (n=54)</td>
<td>10 (n=54)</td>
<td>10 (n=54)</td>
<td>10 (n=54)</td>
<td>10 (n=54)</td>
<td></td>
</tr>
<tr>
<td>Any event</td>
<td>75</td>
<td>5</td>
<td>67</td>
<td>17</td>
<td>78</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>24</td>
<td>0</td>
<td>22</td>
<td>0</td>
<td>35</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>10</td>
<td>2</td>
<td>13</td>
<td>2</td>
<td>13</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>10</td>
<td>0</td>
<td>9</td>
<td>2</td>
<td>11</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>9</td>
<td>0</td>
<td>7</td>
<td>0</td>
<td>13</td>
<td>0</td>
<td></td>
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<tr>
<td>Diarrhea</td>
<td>3</td>
<td>0</td>
<td>11</td>
<td>0</td>
<td>15</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Appetite decreased</td>
<td>3</td>
<td>0</td>
<td>13</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td></td>
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<tr>
<td>Dry mouth</td>
<td>3</td>
<td>0</td>
<td>6</td>
<td>0</td>
<td>11</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Dry skin</td>
<td>2</td>
<td>0</td>
<td>6</td>
<td>0</td>
<td>13</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>17</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>2</td>
<td>0</td>
<td>7</td>
<td>0</td>
<td>15</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>
### Treatment-related select adverse events

<table>
<thead>
<tr>
<th>Category, %</th>
<th>Nivolumab, mg/kg</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Any grade</td>
<td>Grade 3/4</td>
<td>Any grade</td>
<td>Grade 3/4</td>
<td>Any grade</td>
</tr>
<tr>
<td>Skin</td>
<td>0.3 (n = 59)</td>
<td>22</td>
<td>0</td>
<td>22</td>
<td>4</td>
<td>28</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>2.0 (n = 54)</td>
<td>5</td>
<td>0</td>
<td>11</td>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td>Endocrine</td>
<td>10 (n = 54)</td>
<td>5</td>
<td>0</td>
<td>11</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>Hepatic</td>
<td></td>
<td>3</td>
<td>2</td>
<td>7</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Pulmonary</td>
<td></td>
<td>5</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Hypersensitivity/infusion reaction</td>
<td></td>
<td>2</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>19</td>
</tr>
<tr>
<td>Renal</td>
<td></td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

- No treatment-related grade 3/4 pneumonitis events or grade 5 events were reported.
Overall survival

Based on data cutoff of March 5, 2014; Symbols represent censored observations.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median OS, months (80% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3 mg/kg</td>
<td>18.2 (16.2, 24.0)</td>
</tr>
<tr>
<td>2 mg/kg</td>
<td>25.5 (19.8, 28.8)</td>
</tr>
<tr>
<td>10 mg/kg</td>
<td>24.7 (15.3, 26.0)</td>
</tr>
</tbody>
</table>

Number of patients at risk

<table>
<thead>
<tr>
<th>Treatment</th>
<th>0.3 mg/kg</th>
<th>2 mg/kg</th>
<th>10 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>At risk</td>
<td>60</td>
<td>54</td>
<td>54</td>
</tr>
<tr>
<td>3 months</td>
<td>56</td>
<td>52</td>
<td>50</td>
</tr>
<tr>
<td>6 months</td>
<td>50</td>
<td>45</td>
<td>47</td>
</tr>
<tr>
<td>9 months</td>
<td>41</td>
<td>42</td>
<td>45</td>
</tr>
<tr>
<td>12 months</td>
<td>37</td>
<td>38</td>
<td>38</td>
</tr>
<tr>
<td>15 months</td>
<td>35</td>
<td>35</td>
<td>32</td>
</tr>
<tr>
<td>18 months</td>
<td>31</td>
<td>32</td>
<td>29</td>
</tr>
<tr>
<td>21 months</td>
<td>27</td>
<td>28</td>
<td>29</td>
</tr>
<tr>
<td>24 months</td>
<td>24</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>27 months</td>
<td>13</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>30 months</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>33 months</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Based on data cutoff of March 5, 2014; Symbols represent censored observations.
Overall survival in phase III trials and nivolumab phase II study

<table>
<thead>
<tr>
<th>Drug</th>
<th>AXIS&lt;sup&gt;1,a&lt;/sup&gt;</th>
<th>INTERSECT&lt;sup&gt;2&lt;/sup&gt;</th>
<th>RECORD-1&lt;sup&gt;3&lt;/sup&gt;</th>
<th>GOLD&lt;sup&gt;4&lt;/sup&gt;</th>
<th>Nivolumab study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axitinib; sorafenib</td>
<td>Temsirolimus; sorafenib</td>
<td>Everolimus; placebo</td>
<td>Dovitinib; sorafenib</td>
<td>Nivolumab; 0.3; 2; 10 mg/kg</td>
<td></td>
</tr>
<tr>
<td>Patients, n</td>
<td>389</td>
<td>512</td>
<td>416</td>
<td>570</td>
<td>168</td>
</tr>
<tr>
<td>Risk group, %&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Favorable</td>
<td>Not stated</td>
<td>19</td>
<td>29</td>
<td>20</td>
<td>33</td>
</tr>
<tr>
<td>Intermediate</td>
<td></td>
<td>69</td>
<td>56</td>
<td>58</td>
<td>42</td>
</tr>
<tr>
<td>Poor</td>
<td>12</td>
<td>14</td>
<td>22</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Prior therapy</td>
<td>Sunitinib</td>
<td>Sunitinib</td>
<td>VEGF</td>
<td>VEGF + mTOR</td>
<td>VEGF ± mTOR</td>
</tr>
<tr>
<td>Line of therapy</td>
<td>2nd</td>
<td>2nd</td>
<td>2nd or higher</td>
<td>3rd or higher</td>
<td>2nd to 4th</td>
</tr>
</tbody>
</table>

<sup>a</sup>Post TKI subset. <sup>b</sup>Total ≠100% due to rounding. <sup>c</sup>95% CI. <sup>d</sup>80% CI.

## Overall survival in phase III trials and nivolumab phase II study

<table>
<thead>
<tr>
<th>Drug</th>
<th>AXIS$^1,a$</th>
<th>INTORSECT$^2$</th>
<th>RECORD-1$^3$</th>
<th>GOLD$^4$</th>
<th>Nivolumab study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Axitinib; sorafenib</td>
<td>Temsirolimus; sorafenib</td>
<td>Everolimus; placebo</td>
<td>Dovitinib; sorafenib</td>
<td>Nivolumab; 0.3; 2; 10 mg/kg</td>
</tr>
<tr>
<td>Patients, n</td>
<td>389</td>
<td>512</td>
<td>416</td>
<td>570</td>
<td>168</td>
</tr>
<tr>
<td>Risk group, %$^b$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Favorable</td>
<td>Not stated</td>
<td>19</td>
<td>29</td>
<td>20</td>
<td>33</td>
</tr>
<tr>
<td>Intermediate</td>
<td></td>
<td>69</td>
<td>56</td>
<td>58</td>
<td>42</td>
</tr>
<tr>
<td>Poor</td>
<td></td>
<td>12</td>
<td>14</td>
<td>22</td>
<td>25</td>
</tr>
<tr>
<td>Prior therapy</td>
<td>Sunitinib</td>
<td>Sunitinib</td>
<td>VEGF</td>
<td>VEGF + mTOR</td>
<td>VEGF ± mTOR</td>
</tr>
<tr>
<td>Line of therapy</td>
<td>2nd</td>
<td>2nd</td>
<td>2nd or higher</td>
<td>3rd or higher</td>
<td>2nd to 4th</td>
</tr>
<tr>
<td>Median OS, months</td>
<td>15.2; 16.5</td>
<td>12.3; 16.6</td>
<td>14.8; 14.4</td>
<td>11.1; 11.0</td>
<td>18.2; 25.5; 24.7</td>
</tr>
<tr>
<td>CI</td>
<td>12.8, 18.3$^c$</td>
<td>10.1, 14.8$^c$</td>
<td>Not stated</td>
<td>9.5, 13.4$^c$</td>
<td>16.2, 24.0$^d$</td>
</tr>
<tr>
<td></td>
<td>13.7, 19.2$^c$</td>
<td>13.6, 18.7$^c$</td>
<td>8.6, 13.5$^c$</td>
<td>19.8, 28.8$^d$</td>
<td>15.3, 26.0$^d$</td>
</tr>
</tbody>
</table>

$^a$Post TKI subset. $^b$Total ≠100% due to rounding. $^c$95% CI. $^d$80% CI.

Immunomodulatory activity of nivolumab in previously treated and untreated metastatic renal cell carcinoma (mRCC): biomarker-based results from a randomized clinical trial

Toni K. Choueiri, Mayer N. Fishman, Bernard Escudier, Jenny J. Kim, Harriet Kluger, Walter M. Stadler, Jose Luis Perez-Gracia, Douglas McNeel, Brendan Curti, Michael Harrison, Elizabeth R. Plimack, Leonard Appleman, Lawrence Fong, Charles G. Drake, Lewis Cohen, Shivani Srivastava, Maria Jure-Kunkel, Quan Hong, John F. Kurland, Mario Sznol

1Dana-Farber Cancer Institute, Boston, MA, USA; 2H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA; 3Institut Gustave Roussy, Villejuif, France; 4Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD, USA; 5Yale Cancer Center, New Haven, CT, USA; 6University of Chicago Medicine, Chicago, IL, USA; 7University Clinic of Navarra, Pamplona, Spain; 8University of Wisconsin-Madison, Department of Medicine, Madison, WI, USA; 9Providence Cancer Center, Providence Portland Medical Center, Portland, OR, USA; 10Duke University Medical Center, Durham, NC, USA; 11Fox Chase Cancer Center, Philadelphia, PA, USA; 12University of Pittsburgh Medical Center (UPMC) Cancer Pavilion, Pittsburgh, PA, USA; 13University of California San Francisco (UCSF) Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA; 14Bristol-Myers Squibb, Princeton, NJ, USA
# Nivolumab mechanism of action: seeking pharmacodynamic and correlative evidence

<table>
<thead>
<tr>
<th>Hypothesis</th>
<th>Expected observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab reactivates T cells, resulting in expansion and tumor-directed migration</td>
<td>↑ in CD3+ and CD8+ cells and transcripts in tumor biopsies</td>
</tr>
<tr>
<td>Cytokines associated with T-cell expansion and migration will be released</td>
<td>↑ in IFNγ signaling in tumor microenvironment and serum (CXCL9a, CXCL10b)</td>
</tr>
<tr>
<td>Pretreatment measures of exhaustion represent a T-cell response that may be stimulated by nivolumab, resulting in antitumor activity</td>
<td>Pretreatment PD-L1 expression on tumor associates with clinical response</td>
</tr>
<tr>
<td>Changes in tumor-directed migration of T cells associates with antitumor activity</td>
<td>↑ in CD3+ and/or CD8+ cells associates with clinical response</td>
</tr>
</tbody>
</table>

---

Study design

- Archival nephrectomy specimen
- Fresh tissue biopsy from a metastasis (baseline)
- Fresh tissue biopsy from a metastasis (C2D8)

mRCC (clear cell) after antiangiogenic therapy (n=67)
- 1-3 prior therapies
- Progressed from most recent therapy within 6 months
- KPS ≥70%

Arm 1
Nivolumab 0.3 mg/kg IV Q3W

Arm 2
Nivolumab 2 mg/kg IV Q3W

Arm 3
Nivolumab 10 mg/kg IV Q3W

Arm 4
Nivolumab 10 mg/kg IV Q3W

Treat until progression or intolerable toxicity

Treatment-naïve mRCC (clear cell) (n=24)
- KPS ≥70%

- Serum and whole blood sampled at baseline and throughout study period

CR, complete response; C2D8, cycle 2, day 8.
## Clinical activity

<table>
<thead>
<tr>
<th></th>
<th>Previously treated (n=67)</th>
<th>Treatment-naïve (n=23)</th>
<th>All (N=90)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nivolumab 0.3 mg/kg (n=22)</td>
<td>Nivolumab 2.0 mg/kg (n=22)</td>
<td>Nivolumab 10 mg/kg (n=23)</td>
</tr>
<tr>
<td>Objective response rate, n (%); (95% CI)(^a)</td>
<td>2 (9) (1.1-29.2)</td>
<td>5 (23) (7.8-45.4)</td>
<td>5 (22) (7.5-43.7)</td>
</tr>
<tr>
<td>Best response, n (%)</td>
<td>Partial response (PR)</td>
<td>2 (9)</td>
<td>5 (23)</td>
</tr>
<tr>
<td></td>
<td>Unconfirmed PR</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Stable disease (SD)</td>
<td>5 (23)</td>
<td>6 (27)</td>
</tr>
<tr>
<td>Progression-free survival rate, % (95% CI)</td>
<td>24 weeks</td>
<td>18 (6-36)</td>
<td>32 (14-51)</td>
</tr>
</tbody>
</table>

- Secondary endpoints: tumor response for all subjects determined as defined by RECIST v1.1 criteria

\(^a\)CR, PR, unconfirmed CR, unconfirmed PR; \(^b\)90 pts were evaluable for response.
Response according to PD-L1 status by IHC

- 56 evaluable fresh pretreatment biopsies:
  - Minimum of 100 tumor cells (DAKO assay; antibody 28-8)
  - PD-L1+ specimens defined by plasma membrane staining on ≥5% of tumor cells
  - 18 of 56 (32%) samples were PD-L1+

- Response rate:
  - PD-L1(+) 4/18 (22%)
  - PD-L1(-) 3/38 (8%)

- 81% (22/27) of matched fresh specimens showed a <5% increase in tumor membrane PD-L1 expression from baseline to C2D8
Tumor T-cell infiltrates at baseline correlate with tumor burden decrease

Moving average; NOT linear regression.
CD3/CD8 multiplexed IHC and tumor T-cell infiltrates

<table>
<thead>
<tr>
<th>Median increase in T cell infiltrates (CD3/CD8 multiplexed IHC), baseline to C2D8 (%)</th>
<th>All</th>
<th>0.3 mg/kg</th>
<th>2 mg/kg</th>
<th>10 mg/kg</th>
<th>10 mg/kg (naïve)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD3+</td>
<td>78%</td>
<td>115%</td>
<td>140%</td>
<td>80%</td>
<td>62%</td>
</tr>
<tr>
<td>CD8+</td>
<td>88%</td>
<td>257%</td>
<td>162%</td>
<td>139%</td>
<td>61%</td>
</tr>
</tbody>
</table>

- Increase in TILs seen in previously treated & treatment-naïve patients, independent of dose levels

Total number of cells counted in region chosen by pathologist (automated software assessment)
Percentage of CD3+, CD8+ and CD3/8+ determined
Baseline and on-treatment tumor T-cell infiltrates (CD3 and CD8): association with response

N=33

Individual responder

Individual nonresponder

Responder median

Nonresponder median
Nivolumab (anti-PD-1; BMS-936558; ONO-4538) in combination with sunitinib or pazopanib in patients (pts) with metastatic renal cell carcinoma (mRCC)

Dose escalation

S + N arm
- S + N2: n=7 pretreated patients
- S + N5: n=7 pretreated patients
- S + N5 expansion: n=19 treatment-naïve patients

P + N arm
- P + N2: n=20 pretreated patients
Baseline patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>S + N (n=33)</th>
<th>P + N (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean (SD)</td>
<td>58.0 (9.1)</td>
<td>56.3 (8.5)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>26 (78.8)</td>
<td>18 (90.0)</td>
</tr>
<tr>
<td>Female</td>
<td>7 (21.2)</td>
<td>2 (10.0)</td>
</tr>
<tr>
<td>MSKCC risk category, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Favorable</td>
<td>8 (24.2)</td>
<td>4 (20.0)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>24 (72.7)</td>
<td>14 (70.0)</td>
</tr>
<tr>
<td>Poor</td>
<td>1 (3.0)</td>
<td>2 (10.0)</td>
</tr>
<tr>
<td>Surgery, n (%)</td>
<td>33 (100)</td>
<td>20 (100)</td>
</tr>
<tr>
<td>Radiotherapy, n (%)</td>
<td>5 (15.2)</td>
<td>10 (50)</td>
</tr>
<tr>
<td>Systemic therapy, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VEGF-TKI</td>
<td>14 (42.4)</td>
<td>20 (100)</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>5 (15.2)</td>
<td>17 (85.0)</td>
</tr>
<tr>
<td>Cytokine</td>
<td>2 (6.1)</td>
<td>0</td>
</tr>
<tr>
<td>mTOR inhibitor</td>
<td>9 (27.3)</td>
<td>10 (50.0)</td>
</tr>
<tr>
<td>Prior lines of therapy, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>14 (42.4)</td>
<td>14 (70.0)</td>
</tr>
<tr>
<td>≥2</td>
<td>0</td>
<td>6 (30.0)</td>
</tr>
</tbody>
</table>
Antitumor activity (per RECIST 1.1)

<table>
<thead>
<tr>
<th></th>
<th>S + N (n=33)</th>
<th>P + N (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed ORR, n (%)</td>
<td>17 (52)</td>
<td>9 (45)</td>
</tr>
<tr>
<td>95% CI</td>
<td>33.5-69.2</td>
<td>23.1-68.5</td>
</tr>
<tr>
<td>Median duration of response, weeks (range)</td>
<td>37.1 (18.1-80+)(^a)</td>
<td>30.1 (12.1-90.1+)(^b)</td>
</tr>
<tr>
<td>Ongoing responses, % (n/N)</td>
<td>59 (10/17)</td>
<td>33 (3/9)</td>
</tr>
<tr>
<td>Best overall response, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>1 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Partial response</td>
<td>16 (48)</td>
<td>9 (45)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>10 (30)</td>
<td>7 (35)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>1 (3)</td>
<td>4 (20)</td>
</tr>
<tr>
<td>Unable to determine</td>
<td>4 (12)</td>
<td>0</td>
</tr>
</tbody>
</table>

\(^a\)Median follow-up 54.7 weeks; \(^b\)Median follow-up 76.5 weeks.
Duration of response defined as time between date of first response and date of disease progression or death (whichever occurs first).
ORR, objective response rate.
### Grade 3-4 treatment-related AEs in ≥ 10% of patients

<table>
<thead>
<tr>
<th></th>
<th>S + N (n=33)</th>
<th>P + N2 (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total patients with an event, n (%)</strong></td>
<td>33 (100)</td>
<td>20 (100)</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>16 (48.5)</td>
<td>5 (25.0)</td>
</tr>
<tr>
<td><strong>Increased ALT</strong></td>
<td>13 (39.4)</td>
<td>5 (25.0)</td>
</tr>
<tr>
<td><strong>Hyponatremia</strong></td>
<td>6 (18.2)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Increased lymphocyte count</strong></td>
<td>6 (18.2)</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td><strong>Diarrhea</strong></td>
<td>20 (60.6)</td>
<td>12 (60.0)</td>
</tr>
<tr>
<td><strong>Increased AST</strong></td>
<td>12 (36.4)</td>
<td>6 (30.0)</td>
</tr>
<tr>
<td><strong>Fatigue</strong></td>
<td>27 (81.8)</td>
<td>12 (60.0)</td>
</tr>
</tbody>
</table>

- Patients with any event (any grade): 53 (100%)
- No grade 5 treatment-related AEs were observed
- Most toxicities were consistent with the known profile of TKIs
Abstract 4504

Phase I study of nivolumab in combination with ipilimumab in metastatic renal cell carcinoma (mRCC)

Mechanism of action

CTLA-4 Blockade (ipilimumab)

PD-1 Blockade (nivolumab)

Activation (cytokines, lysis, proliferation, migration to tumor)

Tumor Microenvironment

MHC, major histocompatibility complex; TCR, T-cell receptor.
CA209-016 (NCT01472081): phase I study design (N + I cohort)

Patients with mRCC:

- Previously treated or treatment naïve
- Randomization

Arm N3 + I1
Nivolumab 3 mg/kg IV +
Ipilimumab 1 mg/kg IV
Q3W x4

Arm N1 + I3
Nivolumab 1 mg/kg IV +
Ipilimumab 3 mg/kg IV
Q3W x4

Continuous
Nivolumab
3 mg/kg IV
Q2W

- Primary endpoint: Safety (AEs, laboratory tests)
- Secondary endpoint: Efficacy (ORR, duration of response, PFS)
- Exploratory endpoint: Response by tumor PD-L1 status
- Study assessments: Tumor response (RECIST v1.1) evaluated at screening, every 6 weeks (first 4 assessments), then every 12 weeks until disease progression

ORR, objective response rate.
TKI cohort presented by Amin A et al. ASCO 2014, Abstract 5010
Nivolumab plus Ipilimumab Treatment administration

- **Dosing schedule:**

  - **Induction:**
    - Dose 1: Nivolumab IV + ipilimumab IV Q3W × 4
    - Dose 2: Nivolumab 3 mg/kg IV Q2W for both arms

  - **Continuous:**

- At induction visits, patients received 2 infusions
  - 1st infusion was always nivolumab (1 or 3 mg/kg)
  - Ipilimumab (1 or 3 mg/kg) infusion was started ≥30 min after completion of nivolumab infusion
### Baseline patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N3 + I1 (n=21)</th>
<th>N1 + I3 (n=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean (SD)</td>
<td>53.2 (8.26)</td>
<td>53.5 (11.24)</td>
</tr>
<tr>
<td>Sex, male, n (%)</td>
<td>17 (81.0)</td>
<td>21 (91.3)</td>
</tr>
<tr>
<td>MSKCC risk category, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Favorable</td>
<td>5 (23.8)</td>
<td>5 (21.7)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>16 (76.2)</td>
<td>18 (78.3)</td>
</tr>
<tr>
<td>Poor</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Radiotherapy, n (%)</td>
<td>7 (33.3)</td>
<td>8 (34.8)</td>
</tr>
<tr>
<td>Systemic treatments, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiangiogenic</td>
<td>17 (81.0)</td>
<td>18 (78.3)</td>
</tr>
<tr>
<td>Cytokine</td>
<td>10 (47.6)</td>
<td>15 (65.2)</td>
</tr>
<tr>
<td>mTOR inhibitor</td>
<td>12 (57.1)</td>
<td>6 (26.1)</td>
</tr>
<tr>
<td>Prior lines of therapy, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>4 (19.0)</td>
<td>5 (21.7)</td>
</tr>
<tr>
<td>1</td>
<td>11 (52.4)</td>
<td>11 (47.8)</td>
</tr>
<tr>
<td>2</td>
<td>3 (14.3)</td>
<td>1 (4.3)</td>
</tr>
<tr>
<td>&gt;2</td>
<td>3 (14.3)</td>
<td>6 (26.1)</td>
</tr>
</tbody>
</table>

- All patients had prior nephrectomy except for 1 in the N3 + I1 arm, and 2 in N1 + I3 arm
<table>
<thead>
<tr>
<th></th>
<th>N3 + I1 (n=21)</th>
<th>N1 + I3 (n=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed ORR, n (%)</td>
<td>9 (43)</td>
<td>11 (48)</td>
</tr>
<tr>
<td>95% CI</td>
<td>21.8-66.0</td>
<td>26.8-69.4</td>
</tr>
<tr>
<td>Median duration of response, weeks (range)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>31.1 (4.1+-42.1+)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>NR (12.1+-35.1+)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ongoing responses, % (n/N)</td>
<td>78 (7/9)</td>
<td>82 (9/11)</td>
</tr>
<tr>
<td>Best objective response, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>0</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Partial response</td>
<td>9 (43)</td>
<td>10 (43)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>5 (24)</td>
<td>8 (35)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>5 (24)</td>
<td>3 (13)</td>
</tr>
<tr>
<td>Unable to determine</td>
<td>1 (5)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>24-week PFS, % (95% CI)</td>
<td>65 (40-82)</td>
<td>64 (41-80)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Due to the high percentage of ongoing responses, median duration of response may be misleading; <sup>b</sup>Median follow-up 36.1 weeks; <sup>c</sup>Median follow-up 40.1 weeks
Duration of response defined as time between date of first response and date of disease progression or death (whichever occurs first).
Change from baseline in target tumor burden

N3 + I1 (n=20)  
N1 + I3 (n=22)

Positive change in tumor burden indicates tumor growth; negative change indicates tumor reduction.
Responders at first assessment (6 weeks):
N3 + I1 = 4/9 (44.4%)
N1 + I3 = 6/11 (54.5%)

Ongoing responders:
N3 + I1 = 7/9 (77.8%)
N1 + I3 = 9/11 (81.8%)

Patients discontinuing treatment (not due to progression) who continued to respond:
N3 + I1 = 3/9 (33.3%)
N1 + I3 = 5/11 (45.5%)

- Median duration of response (DOR) for N3 + I1 was 31 weeks
- Median DOR was not reached in the N1 + I3 arm at 40.1 weeks follow-up
# Nivolumab plus Ipilimumab

## Treatment-related AEs

<table>
<thead>
<tr>
<th></th>
<th>N3 + I1 (n=21)</th>
<th>N1 + I3 (n=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total patients with an event, n (%)</strong></td>
<td>16 (76.2)</td>
<td>23 (100)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11 (52.4)</td>
<td>16 (69.6)</td>
</tr>
<tr>
<td>Rash</td>
<td>8 (38.1)</td>
<td>4 (17.4)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>6 (28.6)</td>
<td>5 (21.7)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6 (28.6)</td>
<td>8 (34.8)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>4 (19.0)</td>
<td>3 (13.0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (19.0)</td>
<td>9 (39.1)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>4 (19.0)</td>
<td>4 (17.4)</td>
</tr>
<tr>
<td>Chills</td>
<td>3 (14.3)</td>
<td>2 (8.7)</td>
</tr>
<tr>
<td>Constipation</td>
<td>3 (14.3)</td>
<td>2 (8.7)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>3 (14.3)</td>
<td>6 (26.1)</td>
</tr>
<tr>
<td>Lipase increased</td>
<td>3 (14.3)</td>
<td>6 (26.1)</td>
</tr>
<tr>
<td>Amylase increased</td>
<td>1 (4.8)</td>
<td>3 (13.0)</td>
</tr>
<tr>
<td>ALT increased</td>
<td>1 (4.8)</td>
<td>9 (39.1)</td>
</tr>
<tr>
<td>AST increased</td>
<td>0</td>
<td>9 (39.1)</td>
</tr>
</tbody>
</table>

- No grade 5 treatment-related AEs were reported.

Hammers et al. JCO 32S; Abstr 4504, 2014
Nivolumab plus Ipilimumab
Treatment-related select AE categories

<table>
<thead>
<tr>
<th>Category, n (%)</th>
<th>N3 + I1 (n=21)</th>
<th>N1 + I3 (n=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Endocrinopathy</td>
<td>3 (14.3)</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal disorder</td>
<td>6 (28.6)</td>
<td>1 (4.8)</td>
</tr>
<tr>
<td>Hepatic</td>
<td>1 (4.8)</td>
<td>0</td>
</tr>
<tr>
<td>Infusion reaction</td>
<td>2 (9.5)</td>
<td>0</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>1 (4.8)</td>
<td>0</td>
</tr>
<tr>
<td>Renal disorder</td>
<td>2 (9.5)</td>
<td>0</td>
</tr>
<tr>
<td>Skin disorder</td>
<td>8 (38.1)</td>
<td>0</td>
</tr>
</tbody>
</table>

- No high-grade pulmonary AEs, including pneumonitis, were observed

Hammers et al. JCO 32S; Abstr 4504, 2014
Nivolumab Next Steps

• Nivolumab is being compared with everolimus in a phase III trial for patients who progressed on VEGF targeted therapy with an overall survival endpoint

• A phase III trial is planned in the first-line setting for nivolumab plus ipilimumab versus sunitinib
Trials to Watch with Other Checkpoint Inhibitors

- A phase II trial is underway for MPDL3280A plus bevacizumab versus MPDL3280A monotherapy versus sunitinib in first line therapy for metastatic RCC (Genentech)

- Phase I trial of MK-3475 plus pazopanib (Merck/GSK) is underway and for MK-3475 plus axitinib (Merck/Pfizer) is planned
MPDL3280A (Anti-PDL1) Inhibits the Binding of PD-L1 to PD-1 and B7.1

• Blocking PD-L1 restores T-cell activity, resulting in tumor regression in preclinical models
• Binding to PD-L1 leaves PD-1/PD-L2 interaction intact and may enhance efficacy and safety
Inhibition of PD-L1 by MPDL3280A leads to clinical activity in patients with metastatic urothelial bladder cancer (UBC)

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PD-L1 Prevalence in Solid Tumors

<table>
<thead>
<tr>
<th>Indication</th>
<th>PD-L1+ (IC)</th>
<th>PD-L1+ (TC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC (n = 184)</td>
<td>26%</td>
<td>24%</td>
</tr>
<tr>
<td>UBC (n = 205)</td>
<td>27%</td>
<td>11%</td>
</tr>
<tr>
<td>RCC (n = 88)</td>
<td>25%</td>
<td>10%</td>
</tr>
<tr>
<td>Melanoma (n = 59)</td>
<td>36%</td>
<td>5%</td>
</tr>
<tr>
<td>HNSCC (n = 101)</td>
<td>28%</td>
<td>19%</td>
</tr>
<tr>
<td>Gastric cancer (n = 141)</td>
<td>18%</td>
<td>5%</td>
</tr>
<tr>
<td>CRC (n = 77)</td>
<td>35%</td>
<td>1%</td>
</tr>
<tr>
<td>Pancreatic cancer (n = 83)</td>
<td>12%</td>
<td>4%</td>
</tr>
</tbody>
</table>

ICs: tumor-infiltrating immune cells.
TCs: tumor cells.
PD-L1+ if ≥ 5% ICs or TCs were positive for PD-L1 staining (Genentech/Roche PD-L1 IHC).
MPDL3280A: Treatment-Related AEs

Safety-evaluable population with UBC in Phase I expansion

<table>
<thead>
<tr>
<th>Patients With UBC N = 68</th>
<th>All Grade n (%)</th>
<th>Grade 3-4(^a) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>39 (57%)</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>8 (12%)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8 (12%)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>8 (12%)</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>6 (9%)</td>
<td>0</td>
</tr>
<tr>
<td>Asthenia</td>
<td>5 (7%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Chills</td>
<td>3 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>3 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>Lethargy</td>
<td>3 (4%)</td>
<td>0</td>
</tr>
</tbody>
</table>

- MPDL3280A was well tolerated in patients with UBC, including the elderly and patients with impaired renal function
- No treatment-related grade 4 or 5 AEs
- No investigator-assessed immune-related toxicities were reported as of the clinical cutoff

\(^a\) Additional treatment-related Grade 3/4 AEs: thrombocytopenia and decrease in blood phosphorus (1 each).
Clinical data cutoff was Jan 1, 2014.
Includes events occurring in $\geq 3$ patients.
Patients with complete responses. Patients with a CR had < 100% reduction of the target lesions due to lymph node target lesions. All lymph nodes returned to normal size per RECIST v1.1.

IC; tumor-infiltrating immune cells.

Responses are investigator assessed, Best response is not known for 7 patients.

Diagnostic/(Dx) PD-L1 positive: IHC 3 (≥ 10% of ICs PD-L1+) and IHC 2 (≥ 5% but < 10% of ICs PD-L1+).

Diagnostic/(Dx) PD-L1 negative: IHC 1 (≥ 1% but < 5% ICs PD-L1+) and IHC 0 (<1% ICs PD-L1+).

Patients dosed by Nov 20, 2013 (≥ 6 wk follow-up) with measurable disease at baseline. Clinical data cutoff was Jan 1, 2014.
MPDL3280A: Tumor Burden Over Time in UBC

- Median duration of response has not been reached
  - 0.1+ to 30.3+ weeks IHC (IC) 2 or 3 and 0.1+ to 6.0+ weeks for IHC (IC) 0 or 1

Best response is not known for 7 patients.
Patients dosed by Nov 20, 2013 (≥ 6 wk follow-up) with measurable disease at baseline and at least 1 post-baseline measurement.
Clinical data cutoff was Jan 1, 2014.
MPDL3280A in urothelial carcinoma

- Low toxicity even in elderly patients
  - No grade 4-5 events
- High efficacy in PDL1 positive patients
  - Primarily related to infiltrating immune cells
- Activity in PDL1 negative patients similar to our standard salvage chemotherapies
- 94% of responders still responding at data cutoff
- Further development is ongoing
  - Large single arm phase II study recruiting at MSK and other centers
Genentech Randomized Phase II trial
Study Design

Study Schema

Randomize ~150 patients 1:1:1
Stratify:
- Prior Nephrectomy (y/n)
- PD-L1 Status (±)
- Motzer Criteria (low, intermediate, high risk)

Arm A
- MPDL3280A q3w (for 1 year) + Bevacizumab q3w (until PD)

Arm B
- MPDL3280A q3w (for 1 year)

Arm C
- Sunitinib 50 mg (4w-on & 2w-off; until PD)

PD = progressive disease; PD – L1 = programmed cell death–1 ligand 1; q3w = every 3 weeks.

a Mandatory biopsy at progressive disease to be eligible for crossover.